Department of Chemistry
University of Helsinki, Finland

Oxidative Dehydrogenations with Carbocatalysts

Dissertation for the degree of Doctor Philosophiae

David Sebastian Casadio

ACADEMIC DISSERTATION

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Supervised by

Dr. Juho Helaja
Department of Chemistry
University of Helsinki
Helsinki, Finland

Reviewed by

Prof. Paolo Pengo
Department of Chemical and Pharmaceutical sciences
Università di Trieste
Trieste, Italy

Dr. Elina Sievänen
Department of Chemistry
University of Jyväskylä
Jyväskylä, Finland

Opponent

Prof. Päivi Mäki-Arvela
Faculty of Science and Engineering
Åbo Akademi University
Turku, Finland

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The chymists are a strange class of mortals impelled by an almost insane impulse  to seek their pleasure among smoke and vapour,  soot and flame, poisons and poverty, yet among all these evils I seem to live so sweetly, that may I die  if I would change ♁ places with the Persian King  .

"Acta laboratorii Chymica Monacensis, seu Physica Subterranea„ di Johann Joachim Becher (1669)

ABSTRACT

Oxidative dehydrogenation (ODH) of organic compounds is among the most important chemical reactions in the production of fine and commodity chemicals. To date, transition metal catalysts dominate the state-of-the-art for ODH reactions and ODH couplings. An appealing strategy is to develop metal-free catalytic protocols as an alternative. This field is currently dominated by carbon nanomaterials. Yet, there are examples in which simple activated carbon materials (AC) are shown to exhibit significant activity in gas-phase dehydrogenation reactions.

In this thesis, liquid phase carbocatalyzed ODH reactions were developed in two research areas. Firstly, a straightforward one-pot methodology was developed to synthesize otherwise difficultly accessible cyclooctatetraenes (COTs) from 2-(benzofuran-2-yl)-1H-indole and related dimers. Secondly, a carbocatalyzed ODH aromatization protocol was developed for dehydrogenation of *N*-heterocycles.

The COT synthesis methodology developed is based on the previously made observation that carbocatalysts were able to mediate the homocoupling of indoles and other heterocycles. The necessity to use acid additives like MsOH to co-catalyze the coupling of O- and S-containing heterorings does not influence the selectivity towards the indole heteroring for the first coupling, allowing to stop the reaction at the monocoupled intermediate or to let it proceed to the COT product, by adding a controlled amount of MsOH.

A second study has been initiated after the observation of an unexpected migration of benzo-heterorings observed during the COT synthetic conditions optimization. This unreported secondary reaction has been itself screened and optimized, highlighting the possibility of shifting the catalyst's selectivity towards it by employing different ratios of a specific carbon material and acid.

Prior to this work, there were some literature reports demonstrating that plain AC can catalyze the dehydrogenation of some heterocycles with comparable or better efficiency than Pd/C. Dehydrogenative aromatization of 1,2,3,4-tetrahydroquinolines have been carried out readily at 90 °C in toluene, while other N-heterocycles such as tetrahydro-β-carbolines have also been dehydrogenated in longer reaction time. Most attractively, 3-(tetrahydroaryl)-2-phenyl-indoles could be dehydrogenated to 3-aryl-2-phenyl-indoles, which opens a transition-metal-free approach for the synthesis of (hetero)biaryls.

Mechanistically, we were able to conclude that quinone groups in carbon materials are important for the catalysis on the basis of material characterization and quinone model compound studies. The role of the acid is more inconclusive, since in principle it could promote both quinoidic oxidations and direct proton catalyzed reactions.

This work shows that oxidized AC materials are able to mediate some important ODH reactions. This metal-free catalytic technology that utilizes atmospheric oxygen as terminal oxidant is compatible with sustainability demands. Still additional efforts are needed to improve the catalyst's efficiency and allow lower catalyst loading, even though the material exhibited satisfactory recyclability in aromatization reactions. Similarly, more studies are needed to expose the mechanistic role of other functional groups than quinones in the carbocatalyzed reactions.

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ABBREVIATIONS & ACRONYMS

AC – Activated carbon

AQ – Anthraquinone

CNTs – Carbon nanotubes

COT – Cyclooctatetraene

CSA – Camphorsulfonic acid

CVD – Carbon vapour deposition

DCM – Dichloromethane

DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DMF – Dimethylformamide

GO – Graphene oxide

rGO – Reduced graphene oxide

HAT – Hydrogen atom transfer

HFIP – Hexafluoroisopropanol

MsOH – Methane sulfonic acid

MW – Microwave heated reaction

NBS – *N*-bromosuccinimide

ND – Nanodiamonds

oAC_{air} – Activated carbon oxidized with air

$oAC_{air(\Delta)}$ – Activated carbon oxidized with air and decarboxylated with heat

oAC_{HNO3} – Activated carbon oxidized with HNO_3

oAC_{NOx} – Activated carbon oxidized with NOx flow

oCNT – Oxidized carbon nanotubes

ODH – Oxidative dehydrogenation

PQ – Phenanthrenequinone

SET – Single electron transfer

TEA – Trimethylamine

TLC – Thin layer chromatography

TMEDA – Tetramethylethylenediamine

TMS – Trimethylsilane

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1 - INTRODUCTION

In the history of chemistry, metals have always dominated the field of both homogeneous and heterogeneous catalysis. Industrial production of chemical commodities such as ammonia,[1] fuels,[2] methanol[3] and many others, generally requires harsh conditions, sustainable only by metal oxides, zeolites or special alloys.[4] These materials, which are able to stay active for years to decades, are practically and/or economically impossible to replace, in most cases, even by organometallic complexes.

The great variety of metallic atoms available, together with the almost infinite possibilities of combining them[4] or tune them with ligands[5] suggests that most likely metals will always dominate the field of catalysis. This is particularly true for industrial production of commodity chemicals, which normally takes place in flow reactors at high temperature. Nowadays, in fact, good recycling procedures have been developed for the most expensive and toxic catalysts, capable of regenerating them even after their irreversible inactivation.[6]

On the other hand, in fine chemicals production, liquid phase batch processes often cause catalyst deactivation and are susceptible of metal leaching. In addition to this, the high price, non-renewability and toxicity of most transition metals used in catalysis is making metal-free alternatives increasingly more appealing for application in this field.

For these reasons, there is high interest in the research community to design and develop metal-free catalytic processes. In this framework, carbon materials have attracted attention for their interesting properties, giving rise to the field known as carbocatalysis.

1.1 - Carbon materials

Differently from an organocatalyst, which is a well-defined organic molecule with catalytic properties, a carbocatalyst consists of a material composed of repetitive units of an elemental allotrope of carbon. During the last century carbon nanostructures have played an important role in the field of renewable and green energy technology. Carbon nanostructures (CNSs), such as graphene (G),[7] carbon nanotubes (CNTs),[8][9] nanodiamonds (ND)[10][11][12] and fullerene are characterized by fascinating mechanical, electronic, optical and thermal properties which can be fruitfully exploited in catalytic reactions (**Figure 1.1**).

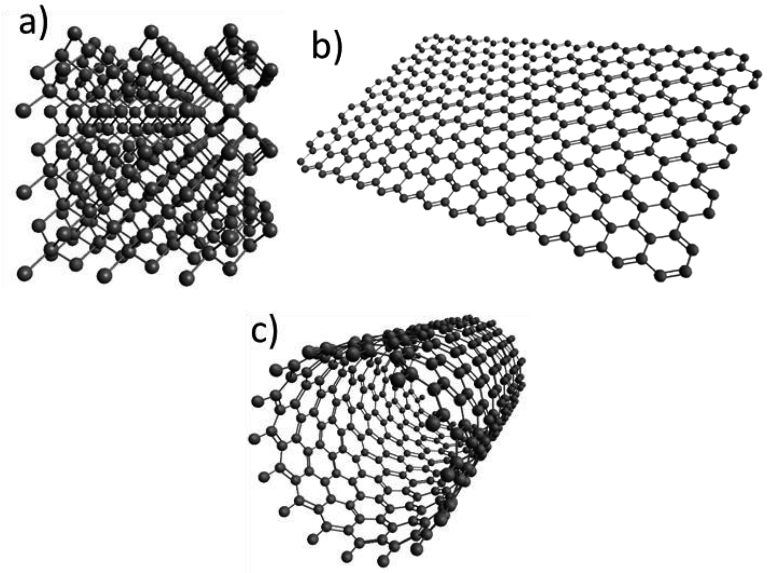


Figure 1.1: Basic structure of a) carbon nanodiamonds, b) graphene, c) carbon nanotubes.

1.1.1 - Graphene

Although the present thesis does not focus on carbon nanomaterials, a few general concepts on graphene will be presented, given that G can be considered, from a structural point of view, as the basic unit of graphitic carbon materials. Graphene was discovered by Novoselov and Geim using a micromechanical exfoliation method in 2004,[13] and thus far it is the thinnest and mechanically strongest material ever measured.[14] G is a two dimensional (2D) allotrope of carbon, composed of a monolayer of carbon atoms arranged in a honeycomb of hexagonal rings.

The key characteristic of graphene is the presence of the p-network, which gives it interesting electronic properties, as well as the ability to adsorb a wide range of radiations, allowing its application, for instance, in photochemistry.

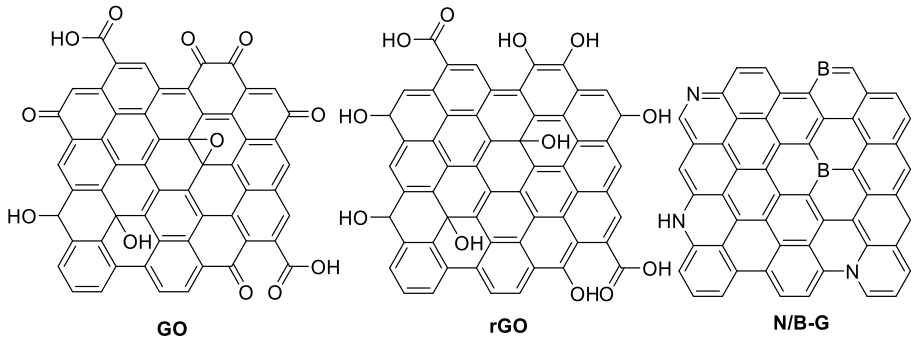
The most common graphitic material employed in catalysis, though, is graphene oxide (GO). GO is an oxygen-rich material obtained by oxidation of graphite, the multilayer form of graphene. The most important and widely applied method for the synthesis of GO was developed by Hummers and Offeman in 1958 (Hummers method).[15] This method consists of the oxidation of graphite in a concentrated H_2SO_4 solution containing $KMnO_4$ and $NaNO_3$. By chemical reduction of GO, generally with hydrazine, reduced graphene oxide (rGO) can be obtained. This graphitic material with different surface properties is also often employed in carbocatalysis (**Scheme1.1**, left and center).[16]

The popularity of GO and rGO is due to the fact that most reactions promoted by carbon materials, occur at defective sites in the honeycomb framework. These

defects are generally located at the material's edges and in proximity of heteroatomic impurities. For this reason, protocols aimed to generate these features in a controlled way have been developed. Oxygen is the most common dopant, and due to its bigger size compared to carbon, it is mainly found as surface functionality, in the form of, for instance, carbonyls, epoxides, acidic moieties, which can promote oxidation reactions.

Other heteroatoms can also be inserted in the carbon matrix deliberately, through the process of doping with N and B, which are the most common dopants. As their size is similar to carbon's, their atoms are mainly integrated the graphitic structure, influencing the electronic properties of the material by generating electron-rich or electron-deficient spots that can activate some redox processes (**Scheme 1.1**, right).

While the functionalization of graphene offers a valuable tool to increase its catalytic performance, identification and characterization of the functional groups remains a non-trivial task.



Scheme 1.1 Examples of graphene surface after different treatments.

1.1.2 - Activated carbon

The origin of activated carbon (AC) can be retraced in Ancient Egypt, where it was initially used for smelting (3750 BC), and later for its adsorbent characteristics employed for water purification and medicinal purposes (1500 BC). In the second half of the 1700's, adsorption of gases on charcoal has been reported for the first time by a Swedish chemist, Karl Wilhelm.[17] In preindustrial times, AC was applied widely as filter, fuel, explosive component[18] and still as reductive agent for metal smelting. However, the potential use of AC was fully capitalized for the first time during the First World War, where it was used as a filter for toxic gases in gas masks. Recently, AC is still abundantly utilized as air purifier, for color removal of industrial and automobile exhausts.

AC is an advanced form of carbon, processed to have many small, low-volume pores that make its surface area very large. This result in its well-known adsorption properties.[19]

AC can be obtained from various biomass sources, making it a cheap, green and renewable material. In order to obtain the characteristic and desirable high surface area, two different activation processes are usually employed.

Physical activation consists of a two-step process. First, the raw material is carbonized in inert atmosphere, after which the activation of the resulting char is obtained at high temperatures in the presence of CO_2, steam or air, which remove part of the carbon atoms by gasification generating porosity.

Chemical activation involves two steps occurring simultaneously: the precursor is impregnated with a chemical agent (an acid or a base, generally) and then pyrolyzed at high temperature. The porogenic effect is due to the chemical reaction of the activating agent with the carbon matrix, and can proceed via dehydration (in the case of acids like $ZnCl_2$ and H_3PO_4) or more complex reactions, as in the case of bases like KOH or NaOH.[19]

The combination of these methods with the vast amount of possible biomass-derived materials that can be used as precursors creates a very broad library of ACs.
It is important to notice that despite this material is defined as amorphous it always shows a certain amount of irregular graphitic layers distributed within its structure. The degree of graphitization varies between differently prepared ACs and depends mainly on the temperature used for the treatment,[20][21] tending to increase with higher temperatures.

While generally this material in its pristine state tends to be less oxygen-rich than other carbon materials generally employed in catalysis like GO,[22] it is possible to increase the oxygen content with both thermal and chemical oxidation protocols making it more interesting for catalytic applications.[23][24] For instance, thermal treatment in the presence of oxygen at temperatures from 300 to 500°C has been shown to increase the amount of oxygen bearing groups on its surface. Chemical oxidants such as nitric acid and hydrogen peroxide, can also be used for this purpose.[25]

1.2 - Carbocatalyzed oxidative reactions

Although the word carbocatalysis has not been used until 2010, carbon was known to be able to catalyze reactions since 1930's.
In the beginning of the 20th century, activated carbon was revealed to be able to catalyze the oxidation of $Fe(CN)_6^{4-}$ to $Fe(CN)_6^{3-}$ using oxygen as terminal oxidant.[26] From then on, a series of studies began, with the purpose of analyzing its chemical properties.
In the same years, graphite started appearing in literature as catalyst for oxidation[27] or reduction[28] reactions. With a more regular structure and higher thermal conductivity, graphite itself without other treatments was reported to have a good

activity in the catalysis of Friedel-Crafts-like alkylations[29] and [4+2] cycloadditions both on anthracene[30] and olefinic species[31].

This different reactivity is due to the diversity of the active sites: the lack of oxygen and the presence of a more extended π-network groups in pristine graphite may explain its affinity with aromatic or olefinic group, which would be activated by a π-stacking interaction.

However, oxidation of graphite to graphene oxide (GO) makes its catalytic activity more similar to the one of AC[32].

This discovery initially favored an increased research interest in this field, however, at industrial level metals were still preferred for these processes. An exception to this trend is the synthesis of phosgene, that is still run industrially on a AC-packed continuous flow reactor.[3]

Additional reasons for the loss of interests into AC development was the disordered, amorphous structure of AC, that makes its characterization quite difficult. Moreover, its uncontrolled production protocols makes its properties batch-related, resulting in it being difficult to study systematically as a catalyst. At the same time, carbon nanomaterials, such as CNTs started to appear in literature, and their defined structures and active sites combined with their durability, which allow the strategic design of highly advanced materials, caused further loss of interest on AC's application in catalysis.

One of the most challenging research goals being currently pursued, though, is to develop functional materials with high catalytic performance in a more sustainable way, from the precursor to the manufacturing. Most of the highly advanced nanocarbon materials, in fact, are typically very expensive and laborious to obtain in their pure form. Their production often involves the employment of metals and, more generally, energy demanding, ecologically unfriendly protocols, which also raise their environmental cost and practical applicability. Moreover, it is not clear yet if they are actually harmful for the human population in the long term.[33]

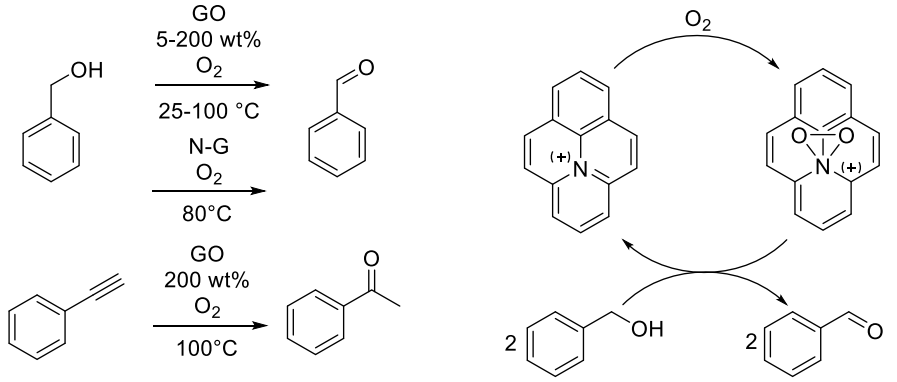
On the other hand, activated carbons (ACs), with their large-scale availability and cheapness, as well as their environmental benignity represent an interesting alternative as metal-free green catalytic materials. As mentioned, in fact, they can be obtained in an operationally easy way by pyrolysis from any carbon-based polymer, including especially the natural ones, such as cellulose, lignin, chitin and various raw biomass materials.[34][35]

1.2.1 – Oxidative dehydrogenations

The most commonly reported reactions catalyzed by carbon materials are oxidative dehydrogenations (ODH). The main reason is the natural abundance of oxygen groups on the surface of carbon materials. These functionalities are hypothesized, in fact, to act as active sites for this type of reactions.

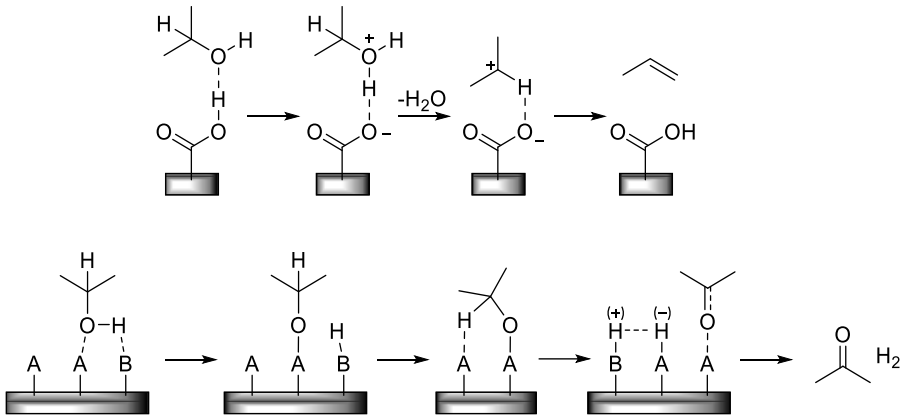
Oxidation of alcohols to aldehydes or ketones as well as hydration of alkynes[36] and some alkenes[32] (**Scheme 1.2**) are examples of reactions that have been reported to be activated by different functional groups on the carbon. While hydration is promoted by the acidic nature of the carbon surface, the oxidation of alcohols has been proven to be catalyzed by epoxidic moieties or by direct activation of O_2 in the presence of a neighboring nitrogen doping atom.[37]

Highly reactive epoxides located on the graphitic layers of GO have shown to be able to oxidize alkanes[38] and, although the possibility to regenerate them by oxygen oxidation of the sp2 bonds has been suggested,[39] their instability can also cause the deactivation of the carbocatalyst, making it act as a stoichiometric reagent.[40]



Scheme 1.2 Left: alcohol and alkyne oxidation. Right: Oxygen activation through N atoms embedded in the graphitic structure.

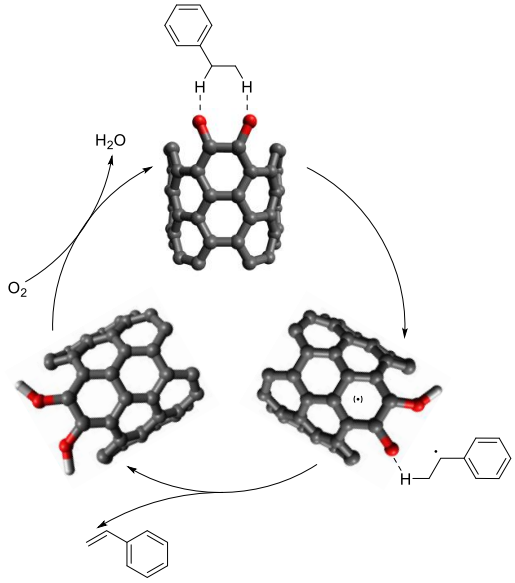
AC has also been reported to be able to both dehydrogenate and dehydrate[41] alcohols (**Scheme 1.3**). While the first reaction follows a typical proton catalyzed mechanism and takes place on acidic sites, the second seems to depend on both Lewis acidic and basic groups. This hypothesis was based on the decrease of activity in alkaline or acidic environment. Selectivity has been reported to depend mainly on the presence and accessibility of acidic groups,[24] a feature that can be regulated by tuning the temperature and method used for the oxidation of AC either by using HNO_3, H_2O_2 or $(NH_4)_2S_2O_8$.



Scheme 1.3 Top: alcohol dehydrogenation with AC. Bottom: alcohol dehydration with AC (A is Lewis acid, B is Lewis base).

Another, more desirable group that has been reported to promote oxidative reactions is the carbonyl. Located at the edges of the carbon materials' graphitic structure, carbonyls and quinones are the most stable among the the oxygen functionalities[42] allowing their employment for catalysis at the same high temperatures used in industrial processes for similar reactions.

This feature allows the dehydrogenation of stable substrates like ethylbenzene,[43] isobutane[44] and butane[45] to olefins (**Scheme 1.4**).



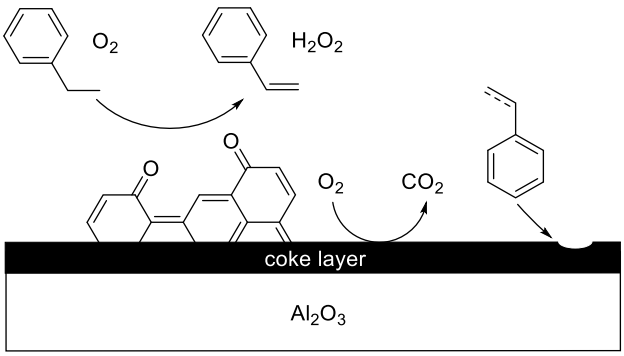
Scheme 1.4 ODH for synthesis of styrene from quinones on CNTs.

The oxidation to alcohols, ketones, acids or epoxides can proceed either via O_2 activation[46][47] by the carbon materials' functional groups or via radicalization of an

aromatic substrate like styrene or tetraline[48] anchored to the carbon surface through π-π stacking. Due to this π-π interaction, rGO has been reported to be capable of activating a stable molecule, such as benzene, for the synthesis of phenol using hydrogen peroxide, instead of O_2, as terminal oxidant.[49]

In the specific case of ethylbenzene it has been shown that inorganic catalysts like alumina, zeolites and metal phosphates develop, with usage, a coke layer that has even better catalytic activity than the original catalyst.[50] While coke formation is common on metallic catalysts and generally causes loss of activity, in this case, carbon deposition and oxidation reaches an equilibrium creating *in situ* a layer of catalytically active carbon.[51]

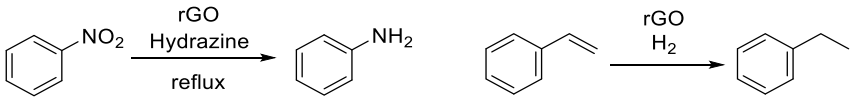
When this process has been then studied with AC and other carbon materials, however, it emerged that microporous AC loses incrementally its activity due to coke deposition, since it reduces the surface.[52] In this case, like for propane and isobutene, carbonyls have been proposed as the main catalytic active sites with a mechanism similar to the one described in **scheme 1.5**.



Scheme 1.5 ODH for synthesis of styrene from coke on Al_2O_3.

1.2.2 - Other reactions

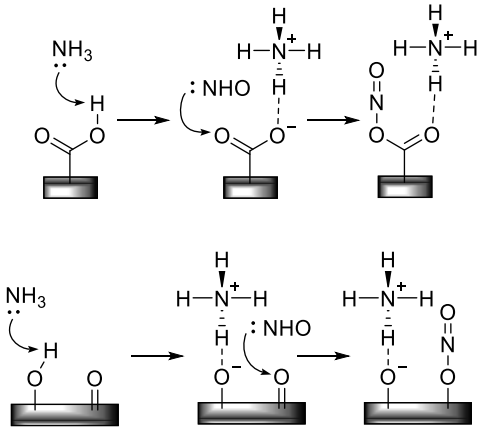
Although most studies concern oxidations, it has been observed that some carbon materials are also able to activate some cheap terminal reductant like hydrogen or hydrazine for the reduction of isolated or conjugated alkene groups as well as for selective hydrogenation of acetylene, alkenes[53] or aryl nitro groups[54] (**Scheme 1.6**).



Scheme 1.6 Reductions catalyzed by rGO with terminal reductant.

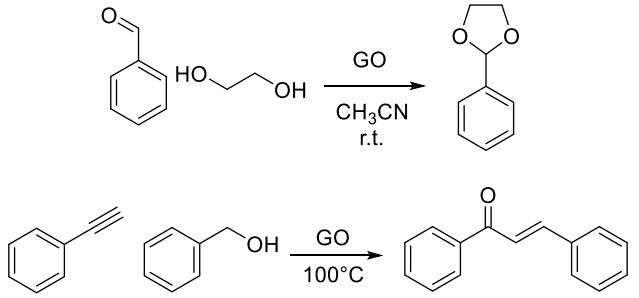
Studies on AC have shown that various treatments may enhance the selective catalytic reduction (SCR) of NOx with NH_3 as terminal reductant. In this case, as well,

oxygen groups seem to be the mostly responsible for the catalytic activity, as proved by the increased activity obtained after HNO_3 and H_2SO_4 treatments.[55] It is however less clear why also *N*-doped ACs show an increased activity.[56] The mechanism proposed is based on the formation of $CO^-(NH_4)^+$ and C(ONO) groups in vicinal positions on the carbon surface, which is supposed to be possible on both acidic sites and vicinal hydroxy-carboxy moieties (**Scheme 1.7**).



Scheme 1.7 SCR catalyzed by AC with terminal reductant.

Carbon materials like GO have also been largely employed as solid acid catalysts. Although the most common acidic group is the carboxylic, sulfonic groups are proposed to be the mainly responsible for acid catalyzed reactions, even when they are present in traces as contaminants, due to Hummer's oxidation protocol, which involves the employment of sulfuric acid[57]. This feature can be used for acid catalyzed reactions like condensations, additions, esterifications and others,[58][59][60] but also in concerted reactions involving multiple active sites[61][62][63] (**Scheme 1.8**).

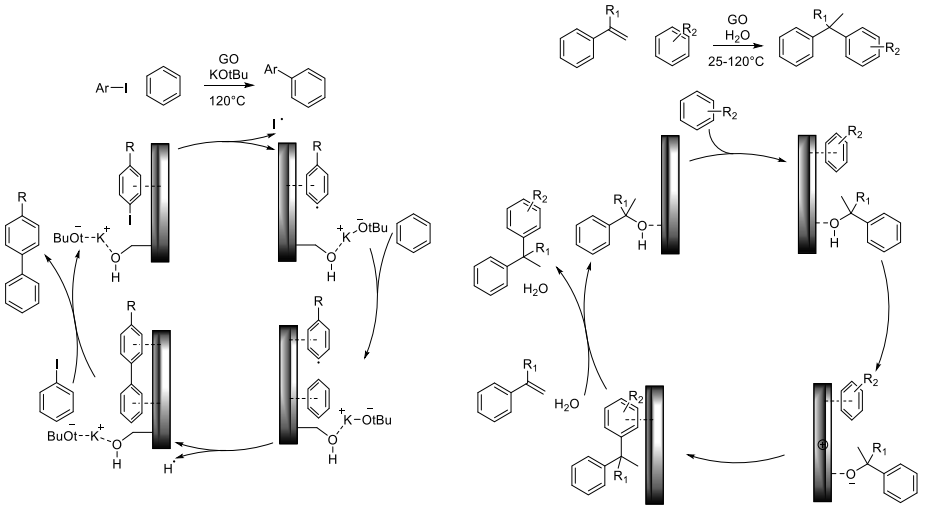


Scheme 1.8 Concerted reaction involving sulfonic acidic groups and oxidative catalytic sites.

Finally, one of the most valuable reactions that can be achieved by these materials, and also in the interests of this thesis, is the coupling. Up to date several types of carbocatalyzed couplings have been observed, such as Friedel-Crafts alkylations,[64]

Michael additions,[65] polymerizations,[66] aromatic heterocouplings[67] and others.[68][69][70][71][72]

Similarly to what happens in other carbocatalyzed processes, when the reaction includes an aromatic compound, the π-π stacking of at least one substrate is generally involved, in addition to other interactions, like the anchoring of the other substrate on the graphitic layer through oxygen groups (**Scheme 1.9**).

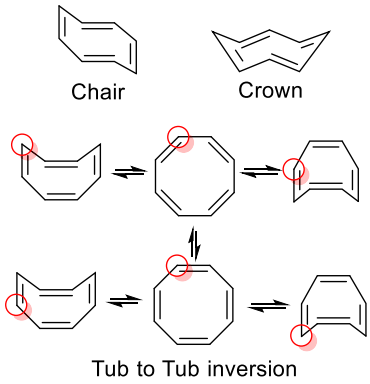


Scheme 1.9 Anchoring and catalysis of aromatic molecules through π-π stacking on graphitic layer.

In conclusion, catalysis with activated carbon is still to be explored, and can offer an interesting, green alternative not only to conventional metal catalysis, but also to the more studied carbon nanostructures.

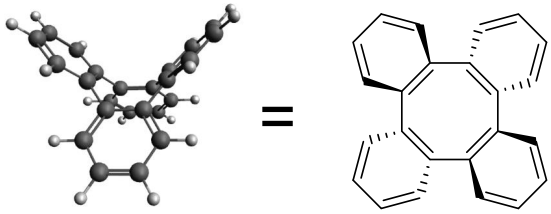
1.3 - Synthesis & properties of cyclooctatetraenes (COTs)

With their particular structure, COTs have various potential applications that are being currently explored. In its neutral configuration, the antiaromatic electronic structure gives to the simplest COT three possible stable conformers.[73] While every conformation has various isomers, the most interesting one is the tub shaped. Differently from the crown and chair shapes, that require solely C=C rotations to transfer directly between each other, the tub shaped is supposed to pass through the planar transition state to invert, or even shift the double bonds before reassuming the tub shape (**Scheme 1.10**).



Scheme 1.10 Conformations of COT.

The presence of groups causing steric hindrance, like aromatic rings, can increasingly destabilize the planar transition state. Two benzannulations[74] exclude completely the crown shaped conformation, and when the benzannulations are vicinal, also the chair shape becomes impossible. Although there are some exceptions,[75] generally tetraphenylenes are rigid even at high temperature (**Scheme 1.11**), while molecules like tetrathiophenes are more flexible.



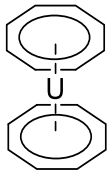
Scheme 1.11 Tub conformation locked by benzoannulations in aromatic COTs.

The presence of aromatic rings makes this kind of COTs different on an additional aspect: the electron shift is no longer possible in the 8-membered ring, since in this case the double bonds are forced in fixed position by the aromatic rings, allowing the ring only to flip through planar state.

This locked structure in the tub conformations shows chirality. Although it shows four atropisomeric bonds each benzene ring influences on both the vicinal bonds. This reduces the conformations to only two of the 16 atropisomeric permutations, independently by the molecular symmetry. This atropisomerism has already shown applications in literature, allowing to build complex chiral structures,[76][77] flexible molecular muscles,[78] and to develop organocatalysts[79] and solar cells.[80]

While the planar structure is unstable in neutral conditions, the removal or addition of an electron can make the COT fit Hückel's rule, generating a 6π or 10π aromatic molecule. Like cyclopentadiene, this form can be used as a ligand for various

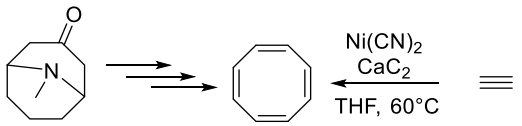
metals[81] [82] especially belonging to the actinide[83] and lanthanide[84] series (**Scheme 1.12**), due to the size of the ring being a better fit for d- and f- orbitals.



Scheme 1.12 Uranocene.

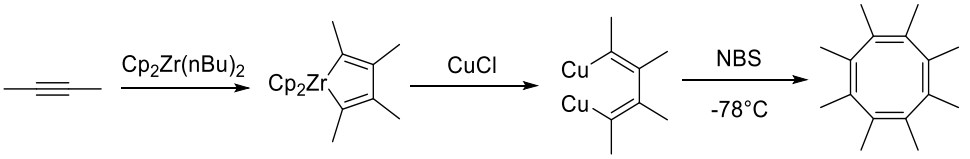
The simplest form of COT and the first one to be synthesized, according to literature, was synthetized starting from pseudopelletierine (**Scheme 1.13**, left) through various steps[85] aiming at the removal of the functional groups while forming the double bonds. Although in this very first procedure a natural product, which already bore the 8-ring cycle structure was used as a starting material, the further developments have adopted a different strategy, where two or more building blocks were assembled into a ring structure.

An improvement of the synthetic protocol of the basic COT was reported a few years later by Reppe, who was able to obtain it by the tetramerization of acetylene[86] in one single step. This more efficient process was already scalable to industrial level and inspired the various other synthetic strategies that have been explored successively.



Scheme 1.13 Left: first synthesis of COT. Right: first single step synthesis of COT.

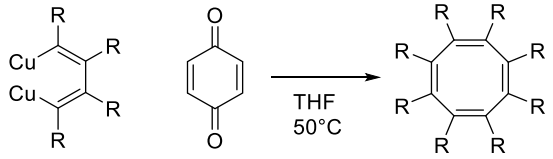
Symmetrically substituted COTs have been obtained with a similar procedure using zirconium-copper transmetallation[87] (**Scheme 1.14**).



Scheme 1.14 Zr catalyzed synthesis of substituted COT.

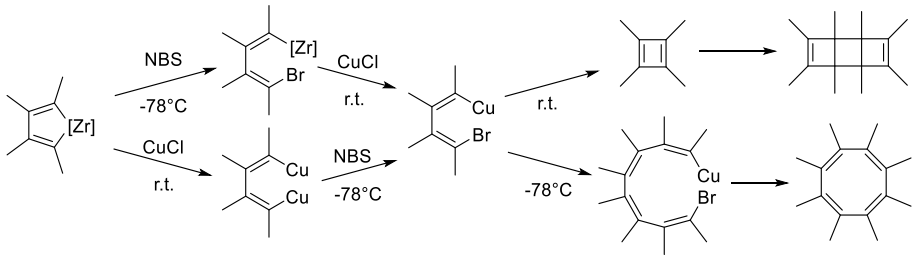
Increasing complexity in the substituents of the COT does not always allow the employment of building blocks with acetylene groups. This issue has been solved with the usage of nBuLi for the first metallation, allowing also the employment of heterocycles with O[88] and S[89][90] as building blocks.

A recent study has shown the possibility of using benzoquinone under mild conditions to allow the final ring closure in substitution of the halogenation[91] (**Scheme 1.15**).



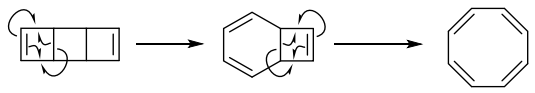
Scheme 1.15 Benzoquinone double oxidative coupling of COT intermediate.

There are actually two mechanisms supported for this final ring closure. Takahashi proposed the formation of a cyclobutadiene followed by dimerization[92] starting from the same halogenated organocopper intermediate that forms the COT (**Scheme 1.16**, bottom products). In his second report, though, the COT was synthesized through a Zr complex. In this case it was claimed that the temperature at which the intermediate is formed determines whether the final coupling is intramolecular or intermolecular, defining in this way the product (**Scheme 1.16**, top products).



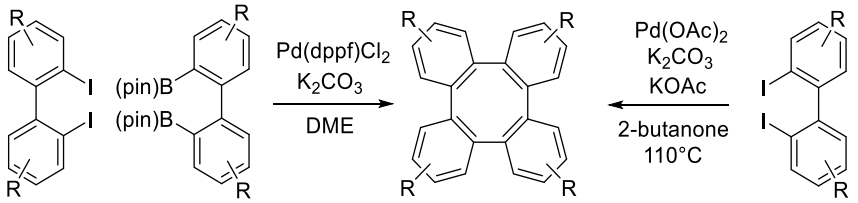
Scheme 1.16 Different synthetic paths with similar reagents.

However, it was previously reported that the rearrangement of cyclobutadiene dimers into COT is possible at a high temperature,[93] suggesting this second mechanism shown in **scheme 1.17**, at least for the benzoquinone mediated process.



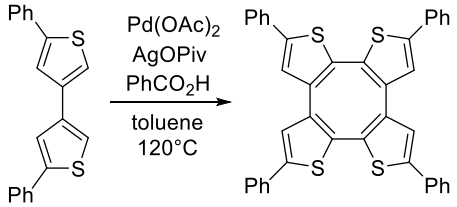
Scheme 1.17 Possible rearrangement of intermediate for synthesis of unsubstituted COT.

Demand for regioselectivity and more complex building blocks pushed researchers into the usage of palladium, initially through Suzuki-Miyaura reactions[94] (**Scheme 1.18**).



Scheme 1.18 Pd-catalyzed synthesis of aromatic COTs.

In further studies, similar catalysts were used to achieve Ullmann-like couplings[95] but also, in some cases, direct C-H activation broadening the scope of palladium catalysis for this application[96] (**Scheme 1.19**).

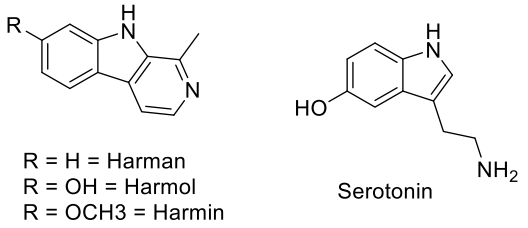


Scheme 1.19 Pd catalyzed synthesis of heteroaromatic COTs.

Concerning pyrrolic heterocycles, there are no literature reports of COTs, except in the indole form. One isomer has been obtained from indolin-2-one using $POCl_3$,[97] the other was developed by our group in higher yields through the concerted gold-oAC catalysis.[98]

1.4 - Synthesis of *N*-heteroaromatics through ODH

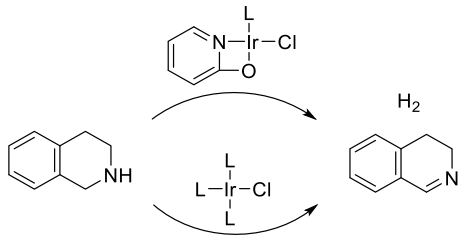
N-heteroarenes represent an important class of compounds that are present in natural molecules and many pharmaceuticals[99] (**Scheme 1.20**).



Scheme 1.20 Examples of bioactive *N*-heteroaromatic molecules.

For their synthesis, one common strategy consists in generating the ring structure through various steps and concluding with its aromatization through dehydrogenation. This final step can occur with direct release of H_2 or with the usage of a terminal oxidant that binds to hydrogen, defining this reaction as direct or oxidative. For *N*-heterocycles the direct dehydrogenation is possible mainly with precious metal catalysts like iridium,[100][101] (**Scheme 1.21**) ruthenium[102] or

palladium[103] complexes in mild conditions, or with more affordable metals[104] [105] in harsher conditions.

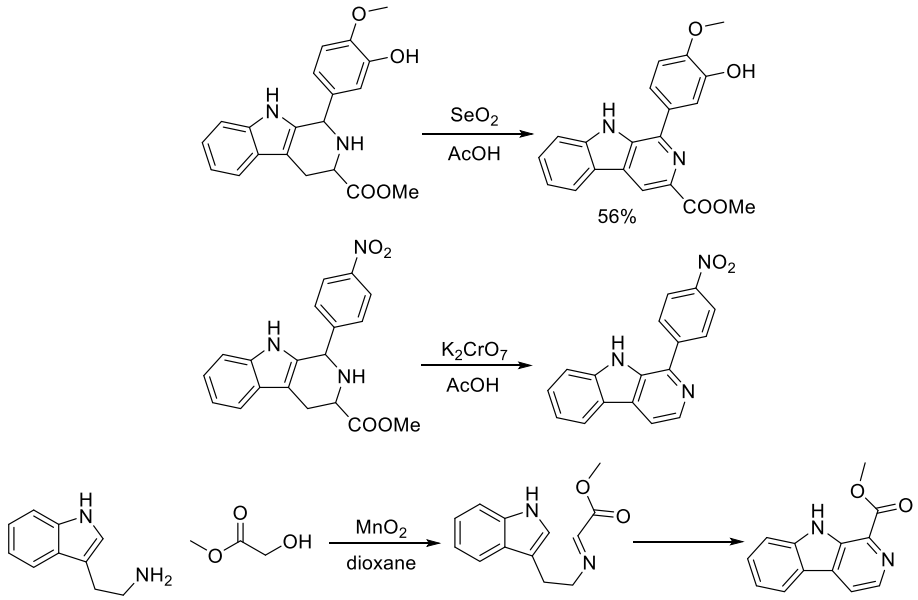


Scheme 1.21 Ir-catalyzed aromatizations of *N*-heterorings with release of H_2.

While these direct oxidations may have excellent yields even in moderately mild conditions, not only do they require the employment of expensive metals, but also tend to be limited to simple substrates.[106]

On the other hand, ODH is more often used, and through time researchers have developed various catalysts that can be applied for the aromatization of highly functionalized *N*-heterocycles. Generally, with this approach, hydrogen is abstracted producing water or other waste products, by reacting with a terminal oxidant and the process is usually mediated by various catalysts.

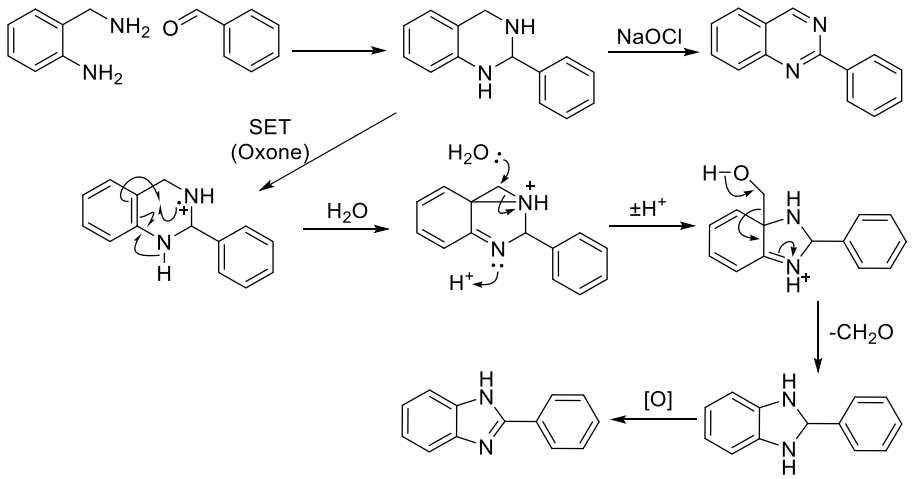
While ODH for aromatization of *N*-heterocycles is quite a simple reaction, the great variety of oxidants suitable and industrially desirable products makes the development of efficient and selective catalysts that are cheap and follow the green chemistry criteria a very hot topic.



Scheme 1.22 Common aromatization of β-carbolines with metal oxidants.

Among stoichiometric oxidants, manganese,[107] selenium[108] and chromium[109] oxides (**Scheme 1.22**) have been the first to be employed to synthesize various bioactive *N*-heterocycles. With its high oxidation potential, K_2CrO_7, and sometimes also SeO_2[110] have been widely used to promote a decarboxylation reaction concerted with the ODH. Manganese has been used not only in its most powerful oxidative form, permanganate, but also as the milder MnO_2. In this case it allowed the buildup of the ring structure and aromatization of β-carboline in a one-pot reaction.[111]

Ring closure and aromatization is a common strategy that has been exploited also with Oxone and NaClO (**Scheme 1.23**). Although in this case it is restricted to rings with two heteroatoms, it gives the possibility to pre-functionalize the two blocks before merging them. Moreover, the different nature of the oxidation mechanism of these two oxidants gives the possibility to selectively produce quinazoline[112] or benzoimidazole[113] [114] from the same starting material.



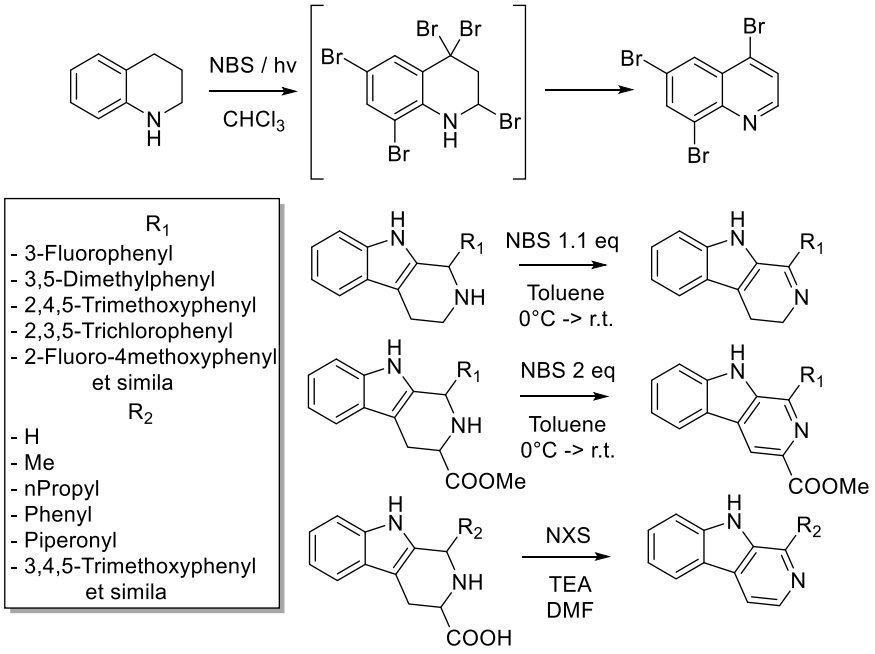
Scheme 1.23 Concerted ring closure and aromatization with NaOCl for 6-ring (top right) or Oxone for 5-ring (bottom).

Halogens like iodine, bromine and chlorine have also been used to abstract selectively hydrogen atoms from heterocycles giving their acids as waste products. *N*-Bromosuccinimide (NBS) is a classic halogenation reagent that generates Br_2 *in situ* when heated, or Br radicals when excited by light. While aliphatic rings may require strong bases to release the hydrogen after halogenation, in the case of quinoline, for instance, the elimination is spontaneous.[115]

While halogenation is sometimes hard to control, the position of nitrogen may direct and limit the regioselectivity, favoring the functionalization of certain carbons on the ring (**Scheme 1.24**, top reaction). A study focused on using these reagents to produce a β-carboline showed that for the substrate presented, the only collateral halogenation happens on the carboxylic group triggering a decarboxylation, like in

the case of chromine,[116] if the group is not esterified (**Scheme 1.24**, centrals and bottom reactions).

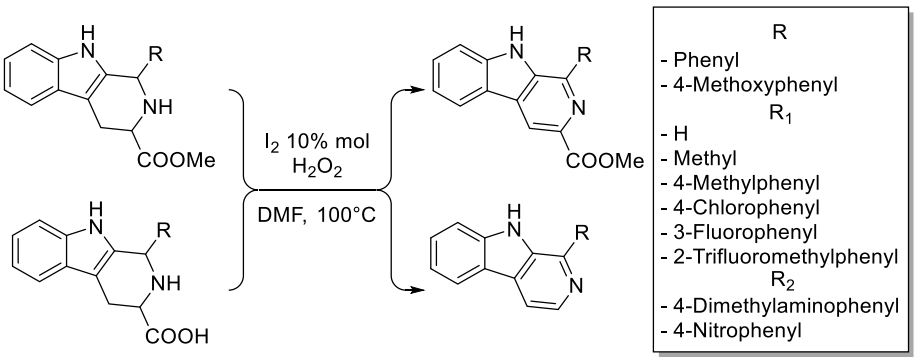
The mechanism proposed consists in a halogen transfer between nitrogens, and further studies showed that this step limits the reactivity and results only in a partial aromatization, that can, however, be completed for some substrates by changing the amount of reagent.[117]



Scheme 1.24 Aromatization through concerted halogenation and elimination.

Elemental halogens, with the exception of iodine, are not used due to their generally uncontrolled reactivity. While Br_2 alone is able to promote the ODH of other kind of substrates, like the coupling of indole,[118] its employment for aromatization of heterorings is limited, as it requires usage of dangerous peroxides and HBr for the *in situ* production of Br_2 and its radicalization.[119]

In the case of I_2 there are not many cases reported in literature. While this reagent has been widely used in oxidative couplings, there are no reports of its employment for the synthesis of quinolones, while for isoquinolines it is used only as a stoichiometric reagent in combination with HgO. Good yields are reported for the synthesis β-carbolines[120] where it is used catalytically with hydrogen peroxide as terminal oxidant, that also regenerates *in situ* I_2 (**Scheme 1.25**).

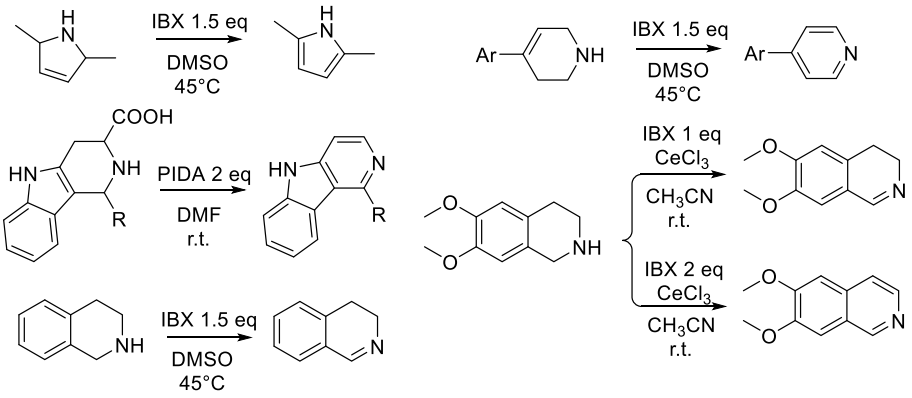


Scheme 1.25 Aromatization with elemental iodine as catalyst and peroxide as terminal oxidant.

Iodine's higher oxidation state allows its application for the aromatization of other *N*-heterorings. Generally used as oxidizing agents, 2-iodoxybenzoic acid (IBX) and (diacetoxyiodo)benzene (PIDA) have been proven to be able to promote the aromatization of secondary amines into products like pyridine, isoquinoline, imidazole[121] and even pyrroles[122] with yields from good to excellent. The addition of a Lewis acid to activate IBX can reduce further the already low temperature required[123] (**Scheme 1.26**).

The mechanism appears to be the same as for the previous I_2/H_2O_2 catalytic reaction, where a direct attack of iodine to the nitrogen is followed by removal of H through the O bonded to iodine. In this case, decarboxylation has been reported as well, at least with PIDA.[124]

As it happens with those promoted by NBS, some of these reactions can be tuned towards single dehydrogenation or complete aromatization. Excluding the exceptional case of secondary decarboxylation, the single dehydrogenation happens when relatively low amounts of oxidant are employed and with substrates that are not functionalized on the aliphatic ring. Functional groups on the aliphatic ring, in fact, stabilize the *N*-heterocycle and promote a subsequent auto-oxidation step which leads to full aromatization.



Scheme 1.26 Partial and complete aromatization of various *N*-heterorings with IBX and PIDA.

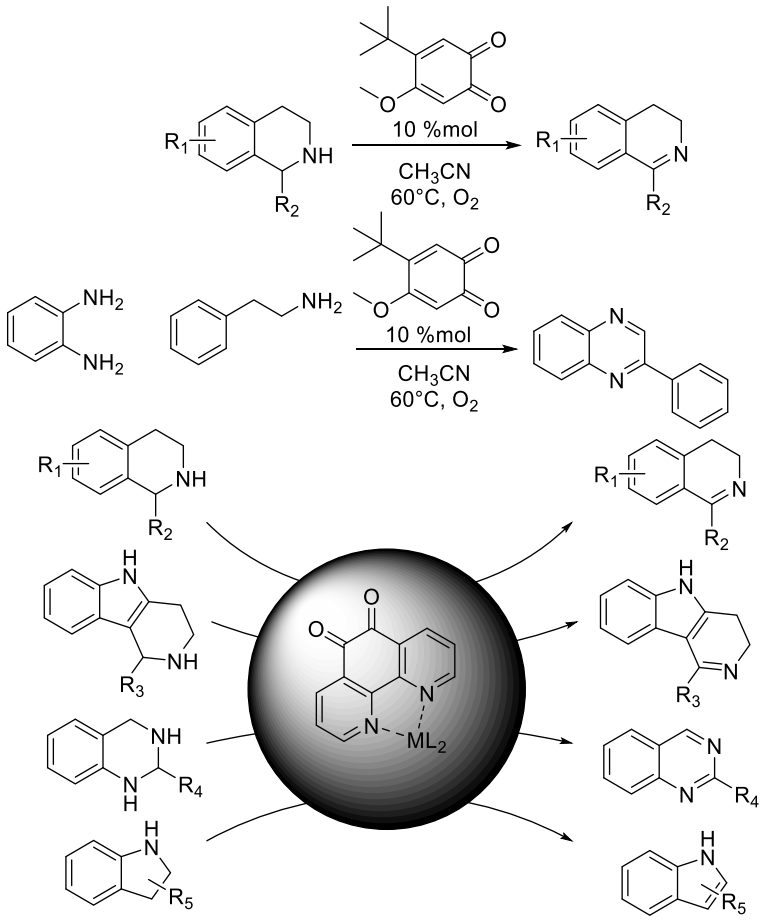
One final elemental oxidant that deserves to be mentioned is sulfur. In relatively harsh condition this multipurpose reagent can be used, in some cases, for the synthesis of β-carbolines[125] and benzimidazoles. Its usage is, though, very limited as it requires being refluxed in xylene and, in presence of imines, it reacts to produce thioamides.

Concerning organic reagents, DDQ and chloranil are the most widely employed for many oxidation reactions. They mostly act as stoichiometric oxidants, but in some cases, it has been proven that they can be regenerated and therefore act as catalysts. In the aromatization of *N*-heterorings there are, however, very few literature reports regarding these high potential oxidants.

The state-of-the-art results in this field have been obtained with two different bioinspired quinones. One of those mimics the behavior of copper amine oxidases by emulating the structure of the bioquinone with a *t*-butyl placed where there should be the linkage with the enzyme. This electron enriched quinone is not as reactive as DDQ and chloranil, and therefore it can be regenerated directly with oxygen. While it is mainly used to oxidize primary amines through a transamination mechanism it has been reported to be able to partially dehydrogenate quinoline, showing to be able to dehydrogenate selectively C-N bonds.[126]

The application of these catalysts is however more suitable for heterocycles with multiple nitrogens.[127]

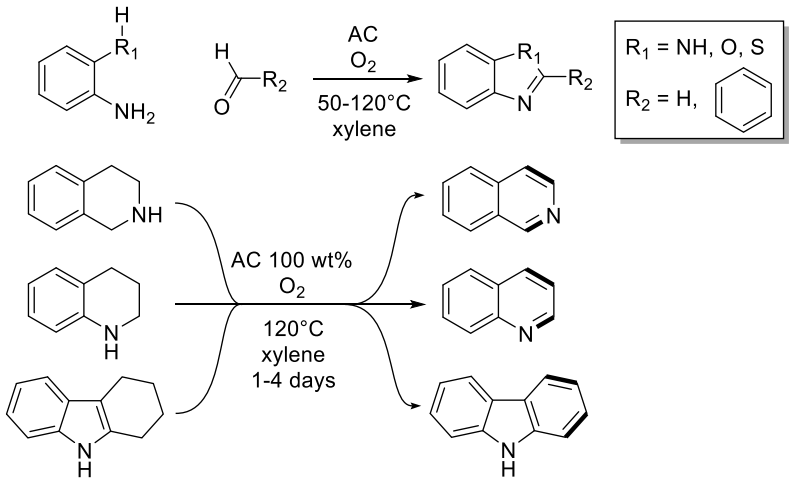
Similarly, the second bio-mimicking quinone has the structure of a 1,10-phenanthroline-5,6-dione with two N atoms opposite to the carbonyls.[128] While the nitrogens are used to chelate a metal atom, the role of the latter lies only in tuning the quinone's electronic properties. The quinone, in fact, remains the catalytically active site in the molecule (**Scheme 1.27**).



Scheme 1.27 Quinone-catalyzed aromatizations of various *N*-heterorings.

Oxidative dehydrogenations of similar N-heterorings have been achieved also by GO and rGO with good yields. Mechanistic investigations confirm epoxides and carbonyls as major active sites, showing also a benefit from a π-conjugated system.[129] Superoxide formation has been detected with rGO, suggesting it as intermediate of catalytic oxygen activation. On the contrary GO doesn't form superoxide but shows a drastic loss of oxygen-containing functional groups,[130] behaving like a stochiometric oxidant.

Finally, also untreated AC and O_2 as terminal oxidant have been employed to obtain various *N*-heterorings like benzazoles,[131][132] 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydrocarbazole.[133]
With a mechanism similar to NaOCl, benzazoles are obtained through amination and intramolecular ring closure catalyzed by AC. The other *N*-heterocycles start from an aliphatic substrate and require harsher conditions and longer reaction time (**Scheme 1.28**).



Scheme 1.28 Aromatization of various *N*-heterocycles catalyzed by untreated AC.

2 - RESULTS AND DISCUSSION

At present various carbon nanomaterials dominate the field of carbocatalysis due to their durability and well-defined structural features. Yet, their catalytic performance has not been sufficient to make their high manufacturing efforts and costs acceptable. ACs are, in fact, commercially available in many forms and they are much more inexpensive than the other carbon (nano)materials. In addition, they are available as high-volume bulk product and they can be prepared from non-fossil feedstock (e.g., lignin, cellulose, agricultural waste, etc.). The aim of this study is to optimize the catalytic performance of AC further and discover new catalytic applications for it. This section is divided into three subsections, which are parts of this monograph presentation, but are also either published, submitted or under preparation articles.

1 - COTs synthesis from 2,2'-bibenzofused heteroaryls by 3,3'-homocoupling of indoles and related benzofused heterocycles

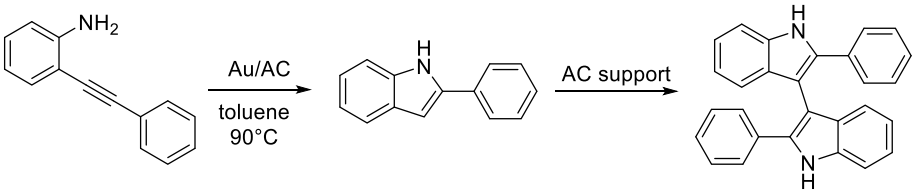
(Major part of these results have been published[134])

2 - oAC and acid catalysed cascade reactions of 2-indole-2-(hetero)aryls: indole homocoupling, de-aromatization, dehydrogenation and (hetero)aryl rearrangement

3 - Oxidative dehydrogenative aromatization of N-heterocycles

(Published[135])

In prior studies, it was discovered that the catalytic activity of partially oxidized AC was notably improved compared to untreated AC. The initial observation of AC catalytic activity was made when it was used as gold catalyst support for indole synthesis from o-alkyl anilines, and some oxidative dehydrogenative (ODH) indole homocoupling products were received (**Scheme 2.1**). It could be identified that the ODH reaction was mediated by the AC, which was oxidized to some extent by aqua regia (HNO_3/HCl 1:3) in the incipient wetness impregnation procedure used to deposit the metal on it.[98]



Scheme 2.1 Gold/AC catalysis cascade for synthesis homocoupled indole.[98]

Subsequently, further research was conducted to optimize the oxidation method of AC to oAC with HNO_3 for the catalytic promotion of homocoupling reactions of benzofused heterocycles. The investigations revealed that the catalysis was mediated both stoichiometrically and catalytically by quinoidic active sites.[136]

The characterization of carbon materials with X-ray photoelectron spectroscopy (XPS) and related deconvolution analysis of the functional groups with reported procedures,[137] in fact, revealed that the amount of carbonyls, singular or quinoidic, was correlated with the catalytic activity. In the study, it was also noticed that oAC had some stoichiometric activity, which was lost after one catalytic cycle. Yet, it was concluded that oAC catalysis has quinoidic character, *i.e.*, quinone groups at the carbon material edges mediate ODH reactions of organic substrates, and the hydroquinones generated in the process are reconverted into quinones via oxidation by atmospheric oxygen.

These pioneering results in liquid phase carbocatalysis of ODH coupling reactions, in combination with the cheap availability of AC, showed the possibility to develop further its catalytic applications aiming at the synthesis of complex molecules in a potentially economic way.

2.1 - COT synthesis by homocoupling of indoles and related benzofused heterocycles

After the discovery of the indole homocoupling activity by oAC and the study of its catalytic mechanism we tried to expand the family of substrates that it could be used with. For this purpose, we used as substrates other heterorings, like benzothiophenes and benzofurans, and tried to reproduce the COT synthesis that was achieved before with bis-indole.

Within the presented research work, a new oxidation protocol to obtain catalytically active AC was developed. This new oAC allowed the discovery of a different reactivity that has been further explored in following projects.

2.1.1 - oAC preparation, analysis and catalytic activity screening

AC was cleaned from metals by HCl washing and used as starting material for the production of oAC_{HNO3}, oAC_{air} and $oAC_{air(\Delta)}$ (**Chapter 3.1**). The carbon materials have been first analyzed with X-ray photoelectron spectroscopy (XPS) to compare the amount and type of oxygen atoms on their surface (**Figure 2.1**).

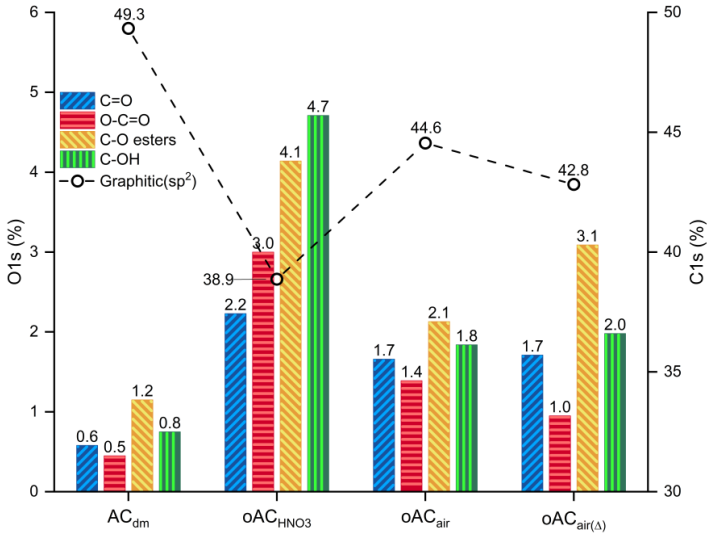


Figure 2.1 Summary of the XPS analysis of the carbon materials.

Material	H_2O	O-C=O	C-O esters	C-OH	C=O	O%
Peak BE (eV)	535.9	524.2	533.3	532.3	531.1	
AC (acid washed)	0.16	0.45	1.15	0.75	0.58	3.09
oAC_{HNO3}	0.42	3	4.14	4.71	2.23	14.5
oAC_{air}	0.28	1.39	2.13	1.84	1.66	7.3
$oAC_{air(\Delta)}$	0.74	0.95	3.09	1.98	1.71	8.47

Table 2.1 Summary of oxygen 1s XPS peak deconvolutions

Material	Graphitic	Aliphatic	C-OH	C=O	O-C=O	C(π-π*)	C%
Peak BE (eV)	284.6	285.2	286.1	287.6	289.1	291.3	
AC (acid washed)	49.33	20.81	8.83	4.75	2.76	7.74	93.73
oAC_{HNO3}	38.83	20.02	8.73	4.53	6.05	5.63	84.59
oAC_{air}	44.55	20.81	11.22	5.3	3.04	7.44	89.32
$oAC_{air(\Delta)}$	42.82	20.68	11.63	5.28	3.26	7.45	87.86

Table 2.2 Summary of carbon 1s XPS peak deconvolutions

oAC_{HNO3} shows the highest oxygen content, although this happens at the expense of the graphitic structure. In contrast, the air oxidation protocol moderately increases the oxygen functionalities, while allowing to better retain the material's structural properties. The deconvolution of the oxygen (**Table 2.1**) peak reveals quite a different functional group distribution in the two different carbon materials: oAC_{HNO3} results to be quite rich in carboxylic acid group compared to oAC_{air}, and the difference is even more accentuated, as expected, if compared to $oAC_{air(\Delta)}$. The thermal treatment in Ar, in fact, reduces the amount of carboxylic groups while not affecting the graphitic content.

To further investigate the oxygen bearing functional groups distribution, oAC_{HNO3} and $oAC_{air(\Delta)}$ were analyzed with temperature programmed desorption (TPD), which can be used to determine the presence and distribution of various oxygen containing functional groups in the bulk of the carbon material (**Figure 2.2**).

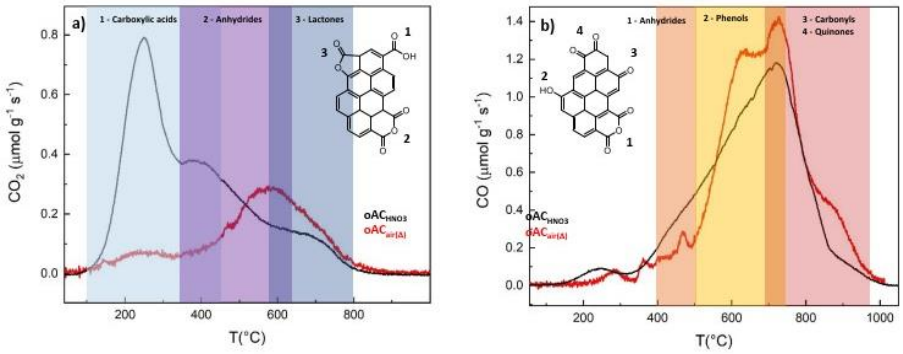


Figure 2.2 Temperature programmed desorption: CO_2 (left) and CO (right) desorption curves of oAC_{HNO3}(black) and $oAC_{air(\Delta)}$ (red)

	Peak 0	**Peak 1**	**Peak 2**	**Peak 3**	**Peak 4**
		Carboxylic anhydrides	Phenols	Carbonyl/ quinones	Pyrones/ Chromenes
T (ºC)	247	453	598	732	893
W (ºC)	106	123	136	136	120
A (µmol/g)	138	540	1370	2074	159

Table 2.3 Deconvolution peaks of CO TPD curve of oAC_{HNO3}

	Peak 1	**Peak 2**	**Peak 3**	**Peak 4**
	Carboxylic acids (strong)	Carboxylic acids (weak)	Carboxylic anhydrides	Lactones
T (ºC)	246	364	453	636
W (ºC)	98	81	123	172
A (µmol/g)	1143	289	540	388

Table 2.4 Deconvolution peaks of CO_2 TPD curve of oAC_{HNO3}

	Peak 1	**Peak 2**	**Peak 3**	**Peak 4**
	Carboxylic anhydrides	Phenols	Carbonyl/quinones	Pyrones/Chromenes
T (ºC)	563	619	731	868
W (ºC)	189	103	103	106
A (µmol/g)	648	1360	1861	619

Table 2.5 Deconvolution peaks of CO TPD curve of $oAC_{air(\Delta)}$

	Peak 1	Peak 3	Peak 4
	Carboxylic acids	Carboxylic anhydrides	Lactones
T (ºC)	260	563	665
W (ºC)	189	189	189
A (µmol/g)	195	648	243

Table 2.6 Deconvolution peaks of CO_2 TPD curve of $oAC_{air(\Delta)}$

The CO_2 desorption curves (**Table 2.4** and **2.6**) confirm the different content of carboxylic acid groups in the two materials, confirming the XPS data. It proves the successful decarboxylation of $oAC_{air(\Delta)}$, where COOH are almost completely absent, while it confirms they're abundant in oAC_{HNO3}. The CO desorption curves (**Table 2.3** and **2.5**) evidence how both materials are rich in carbonyls, although the presence of an additional shoulder at higher temperature (> 800 °C) in $oAC_{air(\Delta)}$ suggests the possible higher content in quinones and basic functionalities, such as chromenes and pyrones.

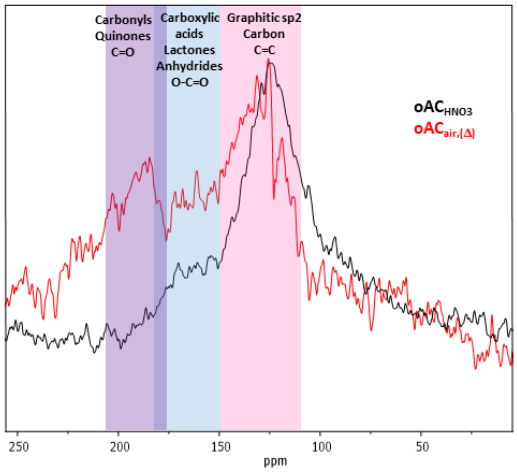
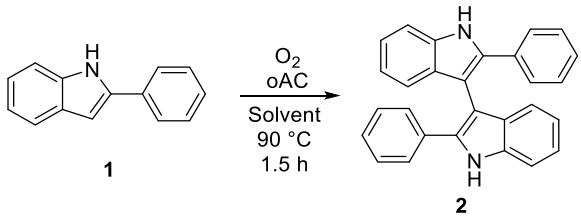


Figure 2.3: MAS NMR of oAC_{HNO3} (black) and $oAC_{air(\Delta)}$ (red)

MAS NMR (**Figure 2.3**) of the materials was also measured. The broad peak appearing around 190-200 ppm for $oAC_{air(\Delta)}$ proves right the assumption of the presence of higher quinones' content.

To evaluate the catalytic activity of each carbon material, the oxidative homocoupling of 2-phenylindole (**1**) was employed as a standard reaction (**Table 2.7**). The tests were performed using 224 mg of oAC per mmol of substrate. The test reactions were run at 90 °C under O_2 atmosphere for 90 minutes. The yield was determined with NMR using 1,3,5-trimethoxybenzene as an external standard.



Entry	Catalyst	Acid	Solvent	Yield (%)	Selectivity (%)[a]
1	oAC_{HNO3}	-	Toluene	38%	73%
2	$oAC_{air(\Delta)}$	-	Toluene	15%	67%
3	oAC_{NOx}	-	Toluene	28%	65%
4	oAC_{HNO3}	MsOH	Toluene	58%	58%
5	oAC_{HNO3}	TsOH	Toluene	37%	55%
6	oAC_{HNO3}	AcOH	Toluene	36%	75%
7	oAC_{HNO3}	-	HFIP	13%	59%[b]

[a] Yield and selectivity are determined with ^{1}H NMR using a capillary external standard. [b] Reaction kept at 58 °C (reflux)

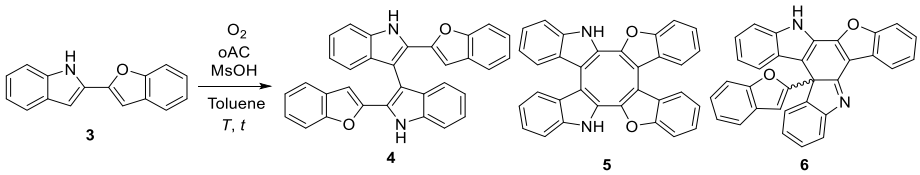
Table 2.7 Study of carbon material activity and additive effect with indole (**1**) to biindole (**2**) coupling reaction as a reference.

oAC_{HNO3} appears to be the most efficient catalyst for this reaction (entry 1), giving 38% yield, oAC_{NOx} being slightly worse in the same conditions (28%) (entry 3), while a very poor yield of 15% is received with $oAC_{air(\Delta)}$ (entry 2). This result is likely due to the higher amount of acidic groups in the nitric acid treated carbon material. Acids are in fact known to boost this reaction. In order to experimentally examine this hypothesis, different acid additives were tested: MsOH, which was already proven effective for this reaction in our previous studies,[136] indeed increased the yield to 58% (entry 4). A weaker acid like AcOH was proven not to be effective at all (entry 6), while a stronger acid like TsOH (entry 2), caused only a slight improvement in yield at expense of the process's selectivity, probably promoting the product's decomposition.

HFIP (entry 7) was tested as solvent for its properties as radical cation stabilizer,[138] to determine if the effect would improve the reaction yield. However, due to its higher volatility compared to toluene, the temperature was kept much lower, leading to lower yield of 13%.

2.1.2 - Screening and optimization

To expand the scope of carbocatalysed COT preparation indole-benzofuran was selected as the substrate.



Entry	Catalyst / Reagent	Catalyst (equiv.)	MsOH (equiv.)	*T* (°C)	Time (h)	Yield (%) **4**:**5**:**6**
1	$oAC_{air(\Delta)}$	1	0	90	24	75 : 0 : 0
2	oAC_{HNO3}	1	0	90	24	80 : 0 : 0
3	oAC_{HNO3}	1	0	100	23	51 : 0 : 0
4	oAC_{HNO3}	1	1	90	23	0 : 10 : 10
5	$oAC_{air(\Delta)}$	1	1	90	23	0 : 20 : 4
6	$oAC_{air(\Delta)}$	2	2	90	3.5	0 : 27 : 0
7	$oAC_{air(\Delta)}$	3	3	90	5	0 : 20 : 0
8	oAC_{HNO3}	3	3	90	5	0 : 0 : 79
9	$oAC_{air(\Delta)}$	5	5	90	1.3	0 : 58 : 0
10	$oAC_{air(\Delta)}$	5	5	70	5	0 : 35 : 0
11	$oAC_{air(\Delta)}$	5	2	90	4.5	0 : 20 : 0
12	oCNT	5	5	90	5	24 : 9 : 7
13	GO	1	1	90	4.5	0 : 0 : 16
14	AQ	1	1	90	24	2 : 0 :0
15	DDQ	1	0	90	1.5	0 : 0 : 0
16	$FeCl_3$	0.1	0	90	23.5	53 : 0 : 0

Table 2.8 Screening and optimization of indole-benzofuran coupling.

First, two different carbocatalysts oAC_{HNO3} and $oAC_{air(\Delta)}$ were tested with the same conditions used for the previous screening (Toluene and oxygen atmosphere): the different catalysts provided solely product **4** in similar yield of respectively 80% (entry 2) and 75% (entry 1) after 24 h. Reducing the reaction time while increasing the temperature with oAC_{HNO3} (entry 3) was proven ineffective, resulting in a lower yield of 51%, suggesting that long reaction times, rather than higher temperatures favor the formation of the homocoupled product **4** (**Table 2.8**).

The addition of MsOH was effective in delivering the desired cyclooctatetraene product, although due to the secondary decomposition reaction taking place over time when acid was added, results in modest yields.

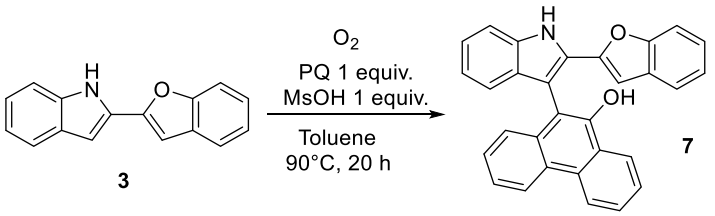
$oAC_{air(\Delta)}$ appears to deliver the desired product **5** in higher yield and with increased selectivity compared to oAC_{HNO3} (entries 4 and 5). The screening conditions shows that reaction time is an important factor, as, to avoid decomposition, higher catalyst

and acid loading and shorter reaction time are preferable. Moreover, increasing the oAC and acid loading in the same ratio has proven to give better results than simply increasing the amount of oAC (entries 6, 7, 9, 10 and 11). Interestingly, when 3 equiv. of MsOH were added to oAC_{HNO3}, 79% yield of an unexpected cyclized 6-ring dearomatized product **6** with a migrated benzofuranyl group was obtained (entry 8), while with $oAC_{air(\Delta)}$ this secondary product disappears with an increase of catalyst and acid loading. This acid co-catalysed oxidative conversion involving aryl migration is thus far unreported, and will be studied in more detail in the next subsection.

Production of **6** shows a diverging selectivity between $oAC_{air(\Delta)}$ and oAC_{HNO3}, which could be related to the great difference in the amount of oxygen functionalities (**Figure 2.1**). With double the amount of carboxylic and alcoholic groups detected, oAC_{HNO3}'s hydrogen bonding may prevent intramolecularly the needed interaction, in the same way as demonstrated by Nakayama with molecular anthraquinone derivatives.[139] This would disfavor the interaction between MsOH and oAC_{HNO3} and favor the interaction between the acid and the substrate while, on the other hand, $oAC_{air(\Delta)}$ would benefit more of the acid interaction with its carbonyls and therefore limit substrate protonation.

Other carbon-based heterogeneous catalysts and homogeneous oxidants that could be able to perform this transformation were tested as a comparison. HNO_3 oxidized CNTs, which have recently been reported to be catalytically active for various intra- and intermolecular ODH couplings in a previous work of this group,[140] though, exhibited lower activity and selectivity for the COT product, even with high catalyst and acid loading, delivering a mixture of **4**, **5**, and **6**, with 24%, 9%, and 7% yields, respectively (entry 12). GO, on the other hand, appears to decompose both the product and the starting material, showing complete selectivity towards the migration product, which is obtained in 16% yield (entry 13).

Molecular quinones such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 9,10-phenanthrene-quinone (PQ), and anthraquinone (AQ) were chosen as models to mimic the carbonylic/quinonic active sites of the carbon materials. For the current reaction, AQ showed very poor activity, delivering only 2% of the monocoupled product **4** (entry 14), while DDQ decomposed the substrate completely after just 1.5 h (entry 15). On the other hand, with PQ, under the same conditions, the catalytic effect is overwhelmed by a direct coupling reaction with the substrate, resulting in a nucleophilic attack from indole's C3 to PQ's carbonyl, which yields the dehydrated product **7** (**Scheme 2.2**). This kind of couplings between indoles and quinones have been previously reported to be Lewis-acid catalyzed at elevated temperatures or photochemical reactions.[141]



Scheme 2.2 Reaction between **3** and PQ.

Iron(III) chloride ($FeCl_3$) is known to be catalytically active in both Scholl-type couplings,[142] and indole homocouplings under oxygen atmosphere.[143] Here, however, $FeCl_3$ only produced **4** with a 53% yield, but failed to produce any COT or migration product (entry 16).

As molecular quinones failed to deliver any distinct product in the reaction conditions (entries 14 and 15, **Table 2.8**), we hypothesized that the presence of the carbon, or possibly the interaction with its surface, is somehow involved in the promotion or stabilization of the different species during the catalytic process. Thus, we tried adding pristine, acid washed AC (448 g/mol of **4**) to the reaction mixture with PQ (1 equiv.) and MsOH (1 equiv.), and ran the reaction using the monocoupled intermediate **4** as the starting material. After running the reaction at 90 °C under Ar over 24 h, **5** and **6** were obtained in 32% and 3% yields, respectively (**Figure 2.4**). Lowering the AC loading to half (224 g/mol of **4**) produced higher conversion but also higher decomposition of **4**, while using a quarter of the amount of AC (112 g/mol of **4**) delivered no **5** and 4% of **6** with modest 35% conversion of SM. As control tests, AC alone, PQ alone, and AC with PQ in the absence of acid did not promote any conversion, while MsOH with AC (224 g/mol of **4**) was able to deliver **5** and **6** in 12% and 8% yield, respectively.

It seems therefore clear that the presence of AC has a beneficial effect on the reaction studied, either by stabilizing the substrates/intermediates/products involved or by lowering the energies related to the rate determining step. This effect can be speculated to arise from the large graphitic surface area correlated with high AC loadings, which favors π-π stacking interactions of the reactive species.[144]

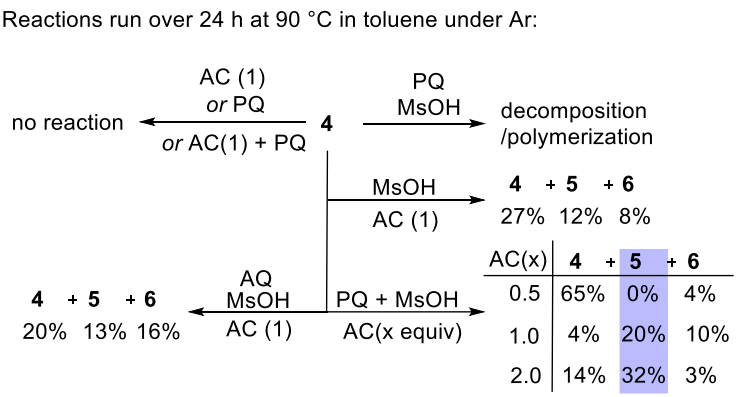


Figure 2.4 Control tests to explore the stoichiometric quinoidic reactivity of **4** in presence of AC (1 equiv. =224 g/mol (of SM)), PQ (1 equiv.) and MsOH (1 equiv.) performed under argon.

To sum up, oAC catalysts have been proven to be far superior in activity and selectivity for this highly sensitive coupling of benzofused heteroarenes in comparison to the other well-known catalysts and oxidants tested, such as $FeCl_3$ and DDQ.

X-ray photoelectron spectroscopy (XPS) has been employed to analyze $oAC_{air(\Delta)}$ after the catalytic production of **5**. **Figure 2.5** reports the deconvoluted O1s peak of the material before and after catalysis. The peak analysis reported in **Table 2.9** shows that the carbonyl content is retained in the process and supports the catalytic nature of the material.

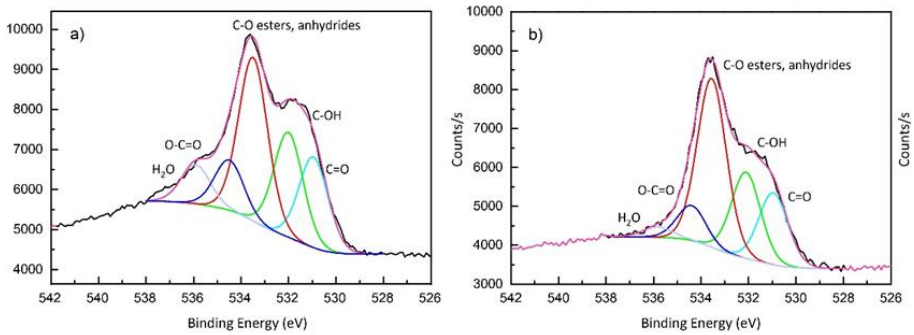


Figure 2.5 XPS of $oAC_{air(\Delta)}$ before (left) and after (right) reaction.

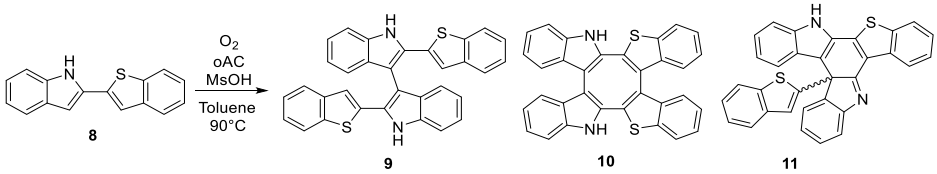
Material	H_2O	O-C=O	C-O esters, anhydrides	C-OH	C=O	N% (pyrrolic)
Peak BE (eV)	535.9	534.2	533.3	532.3	531.1	400.33
$oAC_{air(\Delta)}$	0.73	0.93	3.04	1.95	1.69	
$oAC_{air(\Delta)}$ recycled	0.26	0.85	4.13	2.11	1.76	1.03

Table 2.9 Comparison of oxygen XPS (surface analysis)

Material	Graphitic	Aliphatic	C-OH	C=O	O-C=O	C(π-π*)
Peak BE (eV)	284.6	285.2	286.1	287.6	289.1	291.3
$oAC_{air(\Delta)}$	41.35	22.46	7.81	7.01	4.37	8.32
$oAC_{air(\Delta)}$ recycled	46.93	19.8	6.38	5.81	3.82	6.96

Table 2.10 Comparison of carbon XPS (surface analysis)

2.1.3 - Scope of the reaction



Entry	Catalyst	Catalyst (equiv.)	MsOH (equiv.)	*T* (°C)	Time (h)	Yield (%) **9** : **10** : **11**
1	oAC_{HNO3}	1	0	90	30	46 : 0 : 0
2	$oAC_{air(\Delta)}$	1	0	90	30	43 : 0 :0
3	oAC_{HNO3}	1	1	90	24	27: 0 : 29
4	$oAC_{air(\Delta)}$	1	1	90	24	14: 0 : 15
5	$oAC_{air(\Delta)}$	1	0.5	70	24	85 : 0 :0
6	$oAC_{air(\Delta)}$	5	5	70	24	0 : 0 : 10
7	$oAC_{air(\Delta)}$	5	2	90	6	0 : 2 : 0

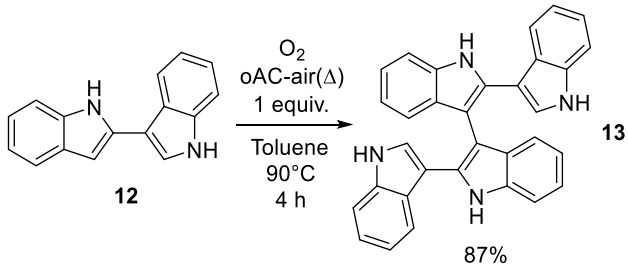
Table 2.11 Optimization of indole-benzothiophene coupling.

In order to expand the scope of this catalytic process, indole-benzofuran **8** was selected as the next target substrate. In the presence of the sole oACs, it was converted to the monocoupled product **9** with a much lower yield compared to **3** in similar conditions (**Table 2.11**, entries 1 and 2), although also in this case, the two carbon materials behaved comparably.

A migration product analogue to the one obtained with **3** was observed for this substrate as well, when oAC_{HNO3} was combined with MsOH (entry 3). In this case, though, the addition of 1 equiv. of MsOH to $oAC_{air(\Delta)}$ also promoted the migration, but with a lower yield causing more decomposition (entry 4). The presence of **9** after 24 h showed a moderate resistance of this intermediate to acid and inspired the decreasing of acid loading and temperature to improve the yield of **9** (entry 5).

The selectivity towards the coupling *via* the benzothiophene groups, which would produce the desired COT, was such a disfavored route that even a higher amount of $oAC_{air(\Delta)}$ and acid would only promote the migration product formation (entry 6), even though in this case the temperature was decreased to limit decomposition of the intermediate.

Reducing the amount of acid in the presence of a high loading of $oAC_{air(\Delta)}$ and keeping the reaction at 90°C for a shorter amount of time resulted in a very low 2% yield of **10,** that allowed its isolation and characterization but could not be improved further (entry 7).

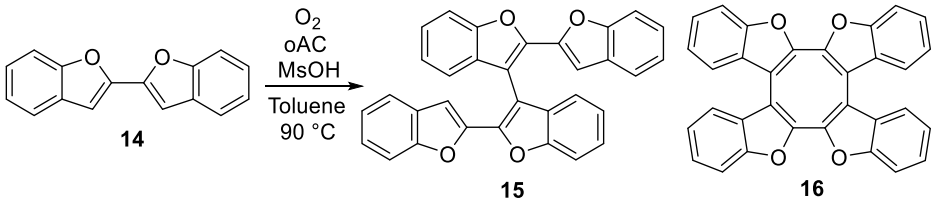


Entry	Catalyst	Catalyst (equiv.)	MsOH (equiv.)	*T* (°C)	Time (h)	Yield (%)
1	$oAC_{air(\Delta)}$	1	0	90	4	87
2	$oAC_{air(\Delta)}$	1	0	90	24	0
3	$oAC_{air(\Delta)}$	1	1	90	1	0

Table 2.12 Synthesis and homocoupling of an asymmetric bis-indole.

A different isomer of bis-indole, **12**, was tested as well (**Table 2.12**). In this case, the only product obtained was the one resulting from the homocoupling reaction between the indoles with the free C3. The reaction was expected due to the higher spin density supposed to be on the free C3 compared to the free C2.[145] However, we were not able to observe any further coupling from the intermediate, as longer reaction time resulted in slow decomposition of the product (entry 2) or fast decomposition when MsOH was added (entry 3).

To further expand the reaction scope, less reactive substrates without the indole group were also tested (**Table 2.13**). In the case of bisbenzofuran substrate **14**, as expected, differently oxidized AC showed different reactivity.

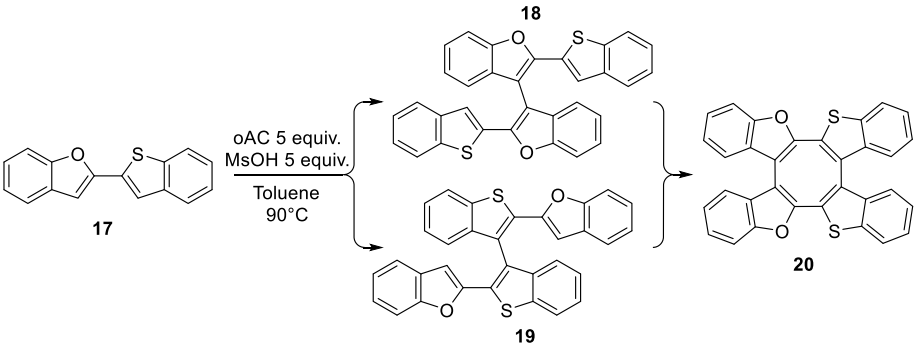


Entry	Catalyst	Catalyst (equiv.)	MsOH (equiv.)	*T* (°C)	Time (h)	Yield (%) **15**:**16**
1	$oAC_{air(\Delta)}$	5	5	90	24	35 : 0
2	oAC_{HNO3}	5	5	70	17	0 : 22

Table 2.13 ODH coupling of bis-benzofuran.

The reaction with the highest loading of $oAC_{air(\Delta)}$ and acid tested, surprisingly delivered only the monocoupled product **15** in modest yield (35%), while when oAC_{HNO3} was employed under the same conditions, 22% of the COT product was obtained selectively.

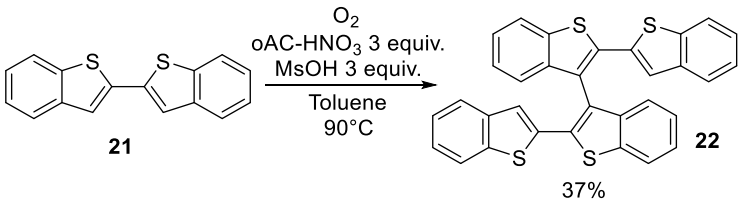
Similarly, benzofuran-benzothiophene showed different reactivity with $oAC_{air(\Delta)}$ and oAC_{HNO3} (**Table 2.14**).



Entry	Catalyst	*T* (°C)	Time (h)	Yield (%) **20**
1	$oAC_{air(\Delta)}$	90	17	0
2	oAC_{HNO3}	70	17	35

Table 2.14 Coupling of benzofuran-benzothiophene.

The COT product **20** could be obtained in 35% yield with 5 equiv. of oAC_{HNO3} and 5 equiv. of MsOH, while $oAC_{air(\Delta)}$ in the same conditions delivered just the monocoupled product as a mixture of **18** and **19**, lacking regioselectivity between the C3 of benzofuran and the C3 of benzothiophene. The structural similarity of the two supposed products did not allow their separation through flash chromatography.



Scheme 2.3 Coupling of bis-benzothiophene.

In the case of bis-benzotiophene (**Scheme 2.3**), even the highest loading of both catalyst and acid failed to deliver the COT product, although a 37% of the monocoupled product could be obtained with oAC_{HNO3}. In this case, the optimal amount of oAC_{HNO3} and MsOH to obtain **22** was found to be 3 equivalents.

2.1.4 - COT properties

Differently from COT **23**, in cyclooctatetraenes formed from benzofused heterarenes the sterical hindrance that allows the formation of stereocenters is located only on 2 sides of the molecule. This reduces the number of atropisomeric bonds from 4 to 2, although the configurations of each of these bonds is not directly influencing the other (**Figure 2.7**). As a result, considering as stereocenters the bonds between the same benzofused heterocycles, a molecule like **5** may have all the 4 possible permutations (S_a-S_a, R_a-R_a, S_a-R_a, R_a-S_a), while centrosymmetric COTs like **16** have a meso form instead of S_a-R_a and R_a-S_a.

For every product however we saw only one set of signals in NMR. We resolved the enantiomers of **5** through chiral column chromatography, analyzed them with circular dichroism (CD) and compared them to the computed spectrum of R_a-R_a.

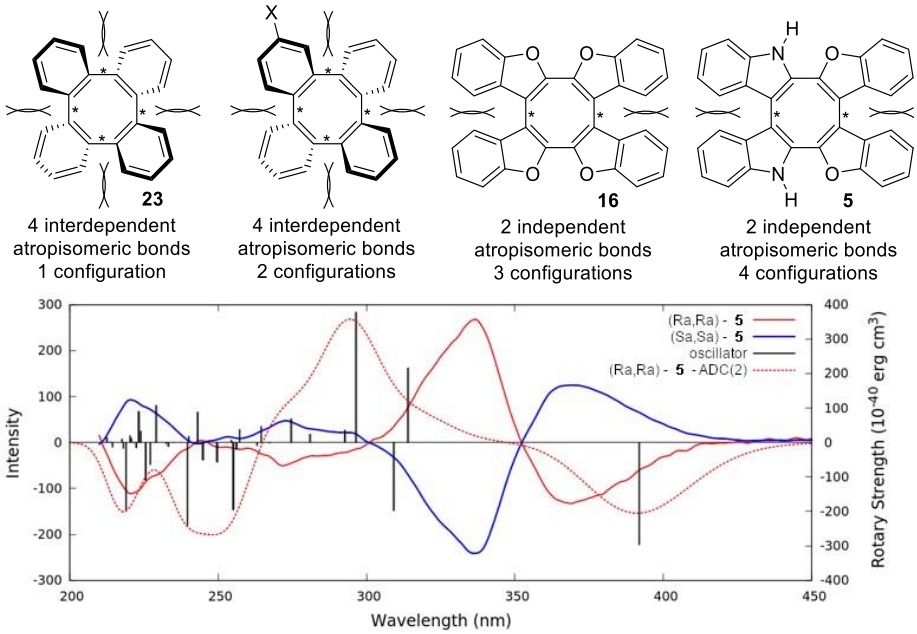


Figure 2.6 Stereocenter comparison (top left). COT **5** (top right). Circular dichroism of **5** with computed (ADC(2)/def2-TZVPPD) spectra (bottom).

The lack of different diasteroisomers or meso forms suggests that the S_a-S_a and R_a-R_a are favored by the promoted mechanistic path and/or that the other forms are unstable.

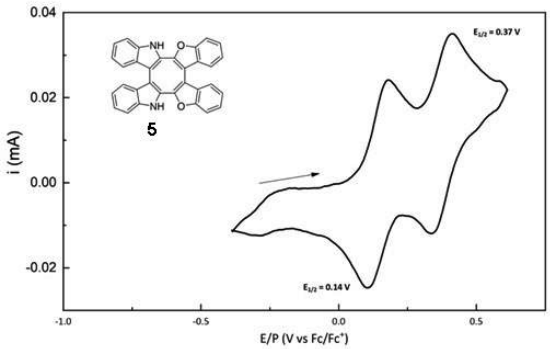


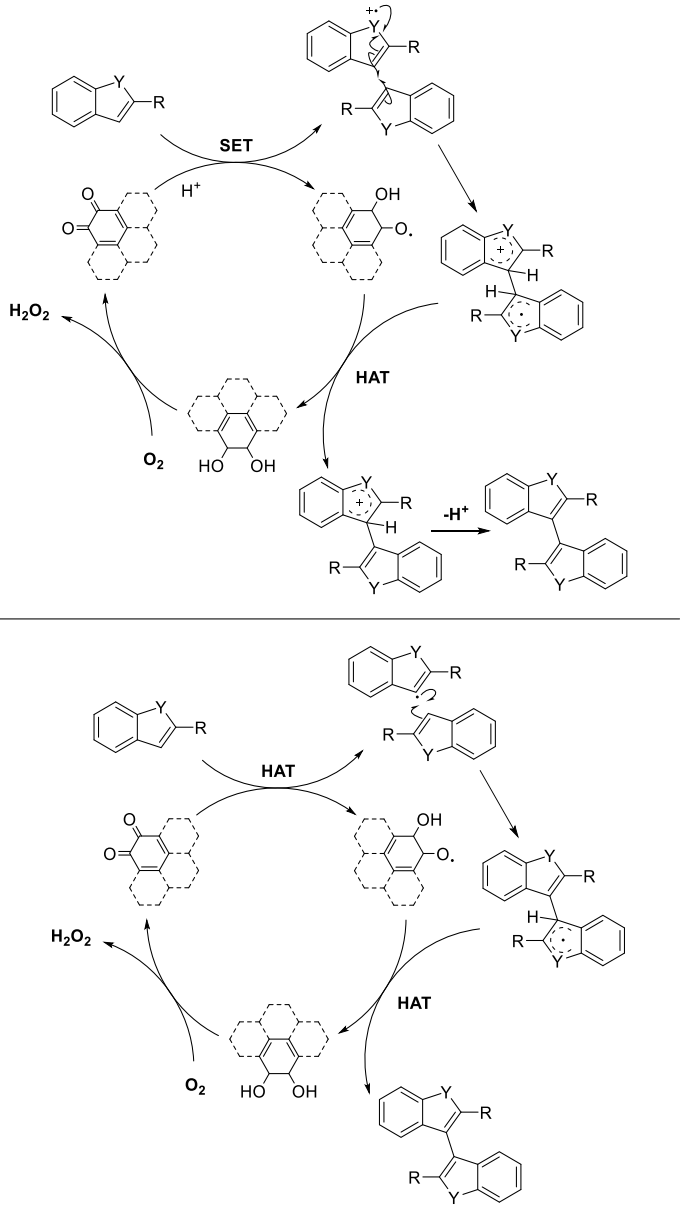
Figure 2.8 CV obtained on GCE in a 0.10 M NBu_4PF_6 solution in acetonitrile under Ar. Scan rate: 0.5 V s^{-1}.

Cyclic voltammetry of **5** in **Figure 2.8** was also measured to evaluate the electrochemical properties of the COT structure, and it revealed two consecutive reversible one-electron oxidations at 0.14 and 0.37 V (vs. Fc/Fc^+). This observation confirms that in the dicationic state, the central COT ring of **5** is aromatic as has been also reported in literature for other COT-structures.[146][147]

2.1.5 - Mechanism

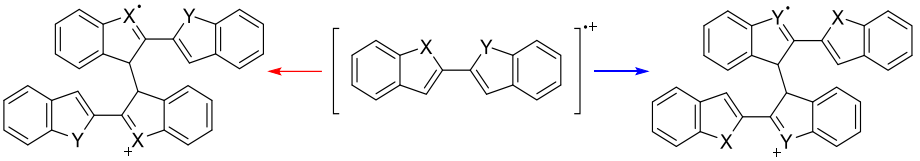
From previous studies[136] we hypothesized that the catalytic active sites are the quinone groups present on the surface of the oACs.

While the mechanism was identified as radical coupling, it has not been possible, so far, to distinguish whether the first step consists of a Single Electron Transfer (SET) or Hydrogen Atom Transfer (HAT). Therefore, specific target substrates were designed to investigate this aspect further (**Scheme 2.4**).



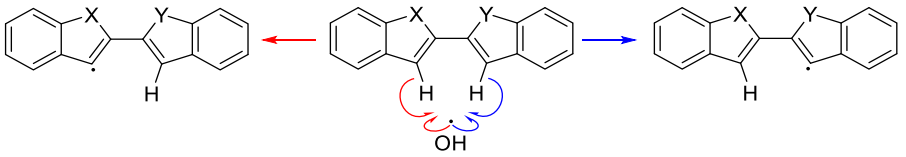
Scheme 2.4 Coupling mechanisms starting with SET (top) or HAT (bottom).

Indole groups bearing substrates would give the same product whether the coupling proceeds through HAT or SET mechanism. However, computational predictions (**Table 2.15** and **Table 2.16**) revealed that *N*-Me-indole coupling would give different products depending on the mechanism followed after the initial radicalization.



Entry	Substrate	X	Y	$\Delta G^{\ddagger}$ X-X (kcal/mol)	$\Delta G^{\ddagger}$ Y-Y (kcal/mol)
1	**8**	S	NH	12.4	**7.1**
2	**3**	O	NH	14.1	**7.2**
3	**S9**	NH	NH	-	**9.8**
4	**24.a**	S	NMe	8.4	**1.7**
5	**24.b**	O	NMe	13.8	**5.4**
6	**24.c**	NH	NMe	10.3	**8.1**

Table 2.15 Transition energies for coupling between a neutral and radical cation. Computational method: PW6B95-D3BJ/def2-TZVPD//PBE0-D3BJ/def2-TZVP, COSMO (Toluene)



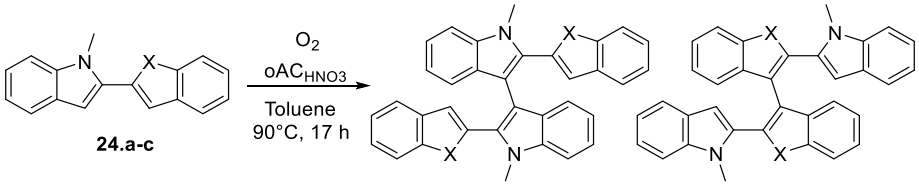
Entry	Substrate	X	Y	$\Delta G^{\ddagger}$ X-H3 (kcal/mol)	$\Delta G^{\ddagger}$ Y-H3 (kcal/mol)
1	**24.a**	S	NMe	**5.9**	6.7
2	**24.b**	O	NMe	8.9	**8.5**
3	**24.c**	NH	NMe	**8.8**	9.8

Table 2.16 Transition energies for HAT using radical OH. Computational method: PW6B95-D3BJ/def2-TZVPD//PBE0-D3BJ/def2-TZVP, COSMO (Toluene)

SET mechanism would proceed by abstracting an electron from the most populated zone, which in both cases would be the indole heterocycle. HAT instead would homolytically break the C-H bond.

The HAT process's transition states predict that in entry 1 and 3 (**table 2.16**) the radicalization shouldn't happen on the NMe-indole moiety, while in entry 2 the energy difference between both radicalizations would be of only 0.4 kcal/mol. According to this prediction, substrates **24.a** and **24.c** would not show a coupling on NMe-indole, while for **24.b** both products could be observed.

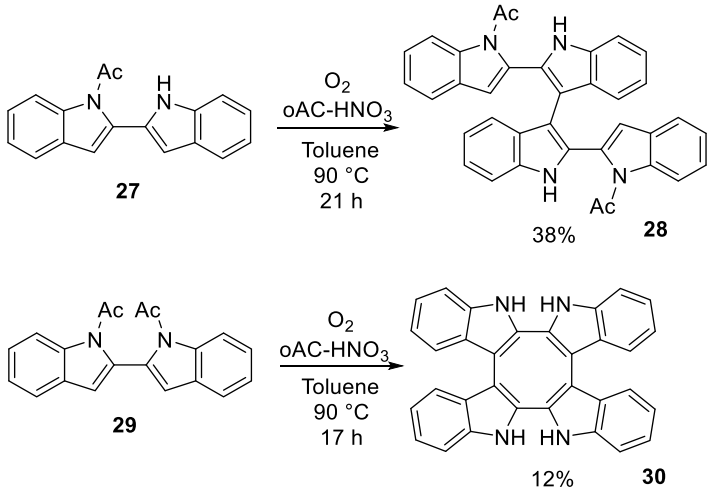
On the other side, SET coupling's transition states predicts that in all cases a coupling on the side of NMe-indole (entry 4, 5 and 6).



Entry	Substrate	Yield (%) **25** : **26**
1	S **a**	52 : 0
2	O **b**	35 : 0
3	NH **c**	36 : 0

Table 2.17 Coupling of *N*-methylated starting materials.

All the tested substrates yielded exclusively the product coupled on the methylated indole side (**Table 2.17**), with no trace of the other possible coupling product, confirming the sole occurrence of the SET mechanism.



Scheme 2.5 Coupling of mono and bi-acylated bis-indoles.

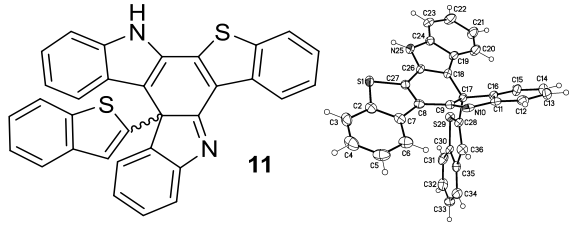
Finally, monoacylated bis-indole was employed to determine whether the absence of the NH proton would interrupt the reaction at the monocoupled intermediate. The reaction performed with N-acylated bis-indole, which has lower electron density compared to the free-NH one, allowed the isolation of the monocoupled product in a moderate yield (38%, **28**) after 21 h (**Scheme 2.5**, top).

The double N-acylated substrate was also tested. We expected that this substrate would not react at all, however, the coupling of **29** took place concerted with the cleavage of the acyl groups, producing the COT **30** in a very low yield (12%) (**Scheme 2.5**, bottom).

2.2 - Indole homocoupling, de-aromatization, dehydrogenation and rearrangement

Upon the synthesis of COTs **5** and **10** (**Table 2.8** and **2.11**), we observed that oAC_{HNO3} in particular, under specific acid catalytic conditions, favored a cascade reaction pathway for the 2-indole-2-heteroaryls, in which, after the indole 3,3'-homocoupling, dearomatization of an indole subring, dehydrogenation and rearrangement of the aryl functionality took place.

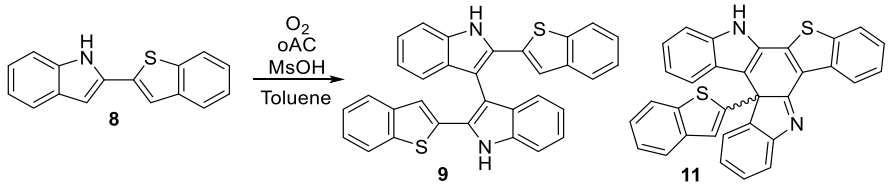
Product **11** was the very first to be obtained and fully characterized with XRD and NMR (**Scheme 2.6**). Therefore, we decided to optimize the reaction conditions to access selectively this new product.



Scheme 2.6 Unexpected product obtained during indole-benzothiophene coupling.

2.2.1 - Screening and optimization

During the optimization carried out for the COT product **10**, we observed for the first time the migration reaction. The selectivity towards the migration product proceeds in similar fashion as for the indole-benzofuran substrate (**Table 2.8**). For simplicity of preparation substrate **8** was used as a target for this optimization.



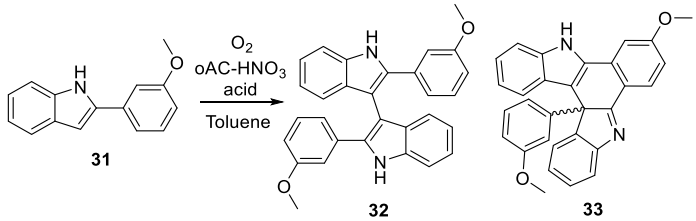
Entry	Catalyst	Catalyst (equiv.)	MsOH (equiv.)	*T* (°C)	Time (h)	Isolated Yield (%) **9 : 11**
1	oAC_{HNO3}	1	1	90	24	27 : 29
2	$oAC_{air(\Delta)}$	1	1	90	24	14 : 15
3	oAC_{HNO3}	2	1	90	16	0 : 40
4	oAC_{HNO3}	2	2	90	16	0 : 42
5	oAC_{HNO3}	3	2	90	16	0 : 41
6	oAC_{HNO3}	3	3	90	16	0 : 29
7	oAC_{HNO3}	4	4	90	4	0 : 26
8	oAC_{HNO3}	4	2	90	4.5	0 : 28
9	oAC_{HNO3}	2	2	70	17	0 : 46
10	oAC_{HNO3}	2	2	50	24	48 : 0

Table 2.18 Optimization of the synthesis of **11**.

As it was confirmed later also with indole-benzofuran, oAC_{HNO3} showed better activity in comparison with $oAC_{air(\Delta)}$ (**Table 2.18**, entries 1, 2). Increasing the acid and carbon loading has also proven to be beneficial for the reaction (entries 3, 4, 5), leading to 42% yield with 2 equivalents of both, the optimal conditions so far.

Increasing acid and/or catalyst loading over 2 equiv. speeds up the SM conversion, lowering reaction times, but also increases the rate of product decomposition, leading to lower yields (entries 6, 7, 8). Lowering the temperature to 70 °C in an attempt to slow down the decomposition slightly improves the yield (entry 9), but when lowered further to 50 °C the migration step did not occur at all (entry 10).

A second substrate bearing an indole ring but without any other heterocycle was tested. Due to the different structure and the higher possibility to expand the scope with this type of a structure, we decided to optimize the conditions to validate them for this new type of substrate, before screening the effect of different acid additives.



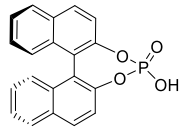
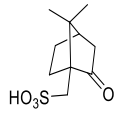
Entry	Catalyst	Catalyst (equiv.)	Acid	Acid (equiv.)	*T* (°C)	Time (h)	Yield (**32** : **33**)
1	oAC_{HNO3}	2	MsOH	2	90	16	0 : 41
2	oAC_{HNO3}	4	MsOH	2	90	2	0 : 26
3	oAC_{HNO3}	2	MsOH	2	70	17	0 : 43
4	oAC_{HNO3}	2	MsOH	2	50	24	24 : 24
5	oAC_{HNO3}	2		2	70	23	36 : 0
6	oAC_{HNO3}	2	TsOH	2	70	18	0 : 17
7	oAC_{HNO3}	2	H_2SO_4	2	70	18	0 : 2
8	oAC_{HNO3}	2		2	70	19	0 : 54
9	oAC_{HNO3}	2	TFA	2	70	19	0 : 8
10	oAC_{HNO3}	2	Chloroacetic acid	2	70	17.5	46 : 0
11	oAC_{HNO3}	2	Dichloroacetic acid	2	70	17.5	11 : 18
12	oAC_{HNO3}	2	Trichloroacetic acid	2	70	17.5	0 : 28
13	oAC_{HNO3}	2	Sulfamic acid	2	70	17.5	46 : 0
14	oAC_{HNO3}	1	-	-	70	30	73 : 0

Table 2.19 Optimization and acid additive screening for the synthesis of **33**.

Employing the conditions just optimized for the previous substrate, 2 equiv. of oAC_{HNO3} and acid at 90 °C, delivered a similar yield of 41% in 16 h (**Table 2.19**, entry 1). As happened with the previous substrate, a higher catalyst loading lowered the yield, probably increasing the product decomposition rate (entry 2). Decreasing the temperature to 70 °C caused a slight yield improvement (entry 3) in this case as well. Lowering it down to 50 °C reduced the yield even further but not as much as with the previous substrate (entry 4).

Next, different acids with this substrate were screened, to determine whether they could be employed to improve the catalyst's activity. First, the enantiopure BNDHP and CSA were tested in an attempt to obtain an enantioselective reaction. Probably due to low acid strength, BNDHP could not catalyze the reaction, producing solely the monocoupled product in low yield (entry 5). CSA, on the other hand, showed better activity than MsOH but no enantioselectivity, producing **33** in 54% yield (entry 8). TFA (entry 9) and H_2SO_4 (entry 7) produced very low yields, presumably due to their excessive strength that promoted the fast decomposition of the indole. Toluene sulfonic acid (entry 6), on the other hand gave better results, but still lower that MsOH, probably due to excessive acid strength, similarly to H_2SO_4. Between the sulfonic acids, the sulfamic acid has shown the lowest activity, yielding 46% of the monocoupled intermediate, possibly due to the insolubility of its zwitterionic form (entry 13).

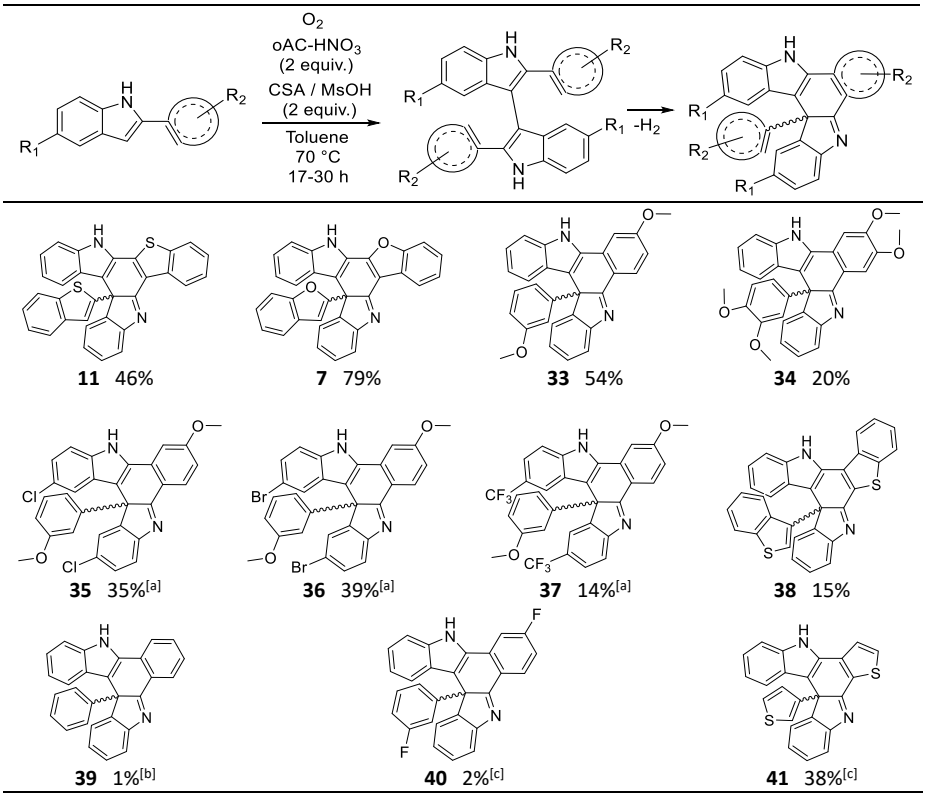
Acetic acids with different level of chlorination were also tested (entries 10, 11 & 12) to compare the effect of the acid strength in acids with similar structures. Although the solvent was toluene we used as a reference for acid strength the pKa in water, supposing that it would be correlated with the pKa in the non-aqueous solvent. The supposedly most active trichloroacetic acid delivers a moderate 28% yield of **33** (entry 12). In the same conditions, weaker dichloroacetic yields 18% of **33** with 11% of **32** (entry 11), while chloroacetic acid produces only 46% of the monocoupled intermediate **32** (entry 10) showing an activity comparable to sulfamic acid.

The indole's sensitivity to acids shows that a certain acid strength is needed to promote the second step of the reaction, however excessive strength causes the undesired decomposition. Weak acids, on the other hand, not only limit the reaction only to the first indole homocoupling (**32**) but also give a lower yield than the reactions with only oAC (entry 14).

Observations made on the results of this optimization made us select the conditions of entry 8 as the general ones: 2 equiv. of racemic CSA, 2 equiv. of oAC_{HNO3} and a temperature of 70 °C.

2.2.2 - Reaction scope

Differently substituted 2-(3-phenyl)-indoles were tested to expand the scope of the catalysed reaction and check its activity in different chemical environments.



[a] reaction at 90°C, [b] reaction with 3 equiv. oAC_{HNO3} and 3 equiv. MsOH, [c] reaction with 2 equiv. MsOH

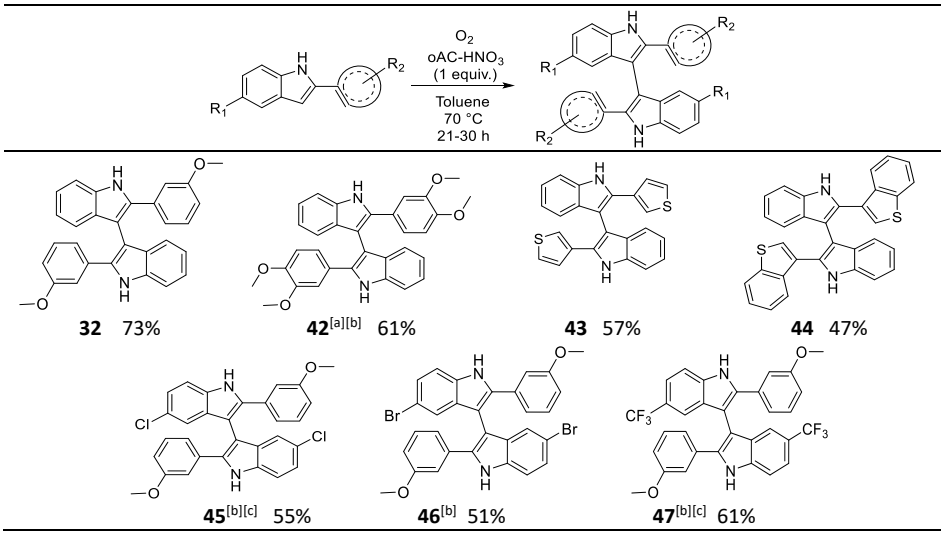
Table 2.20 Coupling and rearrangement of various substrates.

When the aromatic group attached to the indole bears no heteroatoms, results show that an EDG is needed to direct the electron density on the proper carbon and achieve the reaction. Halogen groups in the same location (**40**), on the other hand, have an opposite effect on the electron density showing almost no reactivity (**39**), similarly to 2-phenyl-indole. EWG on the indole ring has a lower influence on the reactivity, which is why the preparation of **35**, **36** and **37** requires harsher conditions. Strong EWG, like the nitro group, can completely block the first step of the reaction, resulting in no reaction. Also, excessive electron density seems to hinder the process (**34**) favoring decomposition, resulting in lower yield.

Indole-thiophene was tested as a substrate as well. The desired product, in this case, was obtained in a moderate yield of 38% (**41**). In comparison with pyrrole and furan, thiophene is relatively inactive towards radical abstraction, and this might be necessary to avoid further coupling following the radical formation.

2.2.3 - Catalysis of other heteroaryl homocouplings

The monocoupled products have been obtained with this catalyst from several different heteroaryls in moderate to good yields (**Table 2.21**).



[a] reaction at 80 °C, [b] reaction with 2 equiv. of oAC_{HNO3}, [c] reaction with 2 equiv. (±)CSA

Table 2.21 Homocoupling of various indole derivatives.

The reaction conditions obtained in the initial optimization had to be modified for some substrates: variation through the parameters of temperature, catalyst loading and acid additive loading led to different optimized conditions for each substrate.

The initial conditions employed were 1 equiv. of oAC_{HNO3} at 70 °C. At these conditions **32** was expected to be obtained more easily than **43** and **44** due to a more electron rich substituent on the C2 of the substrate's indole. At the same time, though, synthesis of **32** required a slightly higher reaction time (30 h) than that of **43** and **44**, for which the starting material was consumed already in 24 h, suggesting that decomposition reactions took place, lowering the yield. A molecule with more EDG like **42** showed higher tendency to decompose. Running the reaction at a higher temperature and with higher catalyst loading (80 °C and 2 equiv. oAC_{HNO3}) shortened the reaction time to 21 h and improved the yield to 61%.

Substrates with an EWG on the indole C5 required harsher conditions and acid additive. For chlorine and CF_3 substituted indoles (**45** and **47**) optimal conditions were found to be 2 equiv. of oAC_{HNO3} and 2 equiv. of (±)-CSA with a 22 h reaction time. At these conditions, the strong inductive effects of CF_3 seemed to have less influence on the reactivity leading to a higher yield of 61% in **47** than the weak inductive effects combined with its resonance of Cl, which lead only to 55% yield in **45**. The Br substituted substrate did not require any acid additive (**46**) to couple and resulted in a yield of 51%. An EWG combining resonance with strong inductive effects

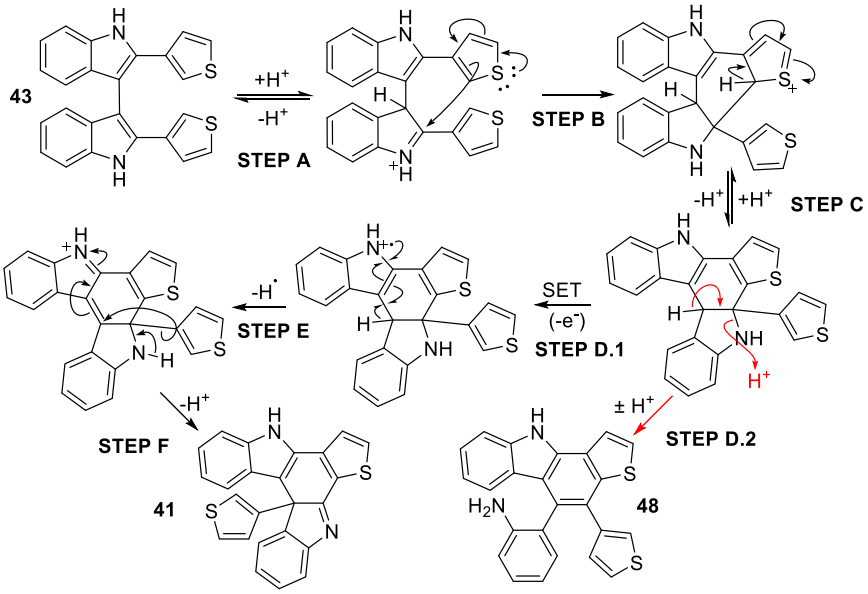
like the nitro group, did not allow the homocoupling to take place at all even at very harsh conditions (130 °C with anisole as solvent).

2.2.4 - Mechanism

The mechanism we hypothesized consists of a triple concerted reaction: the mechanism for the first coupling step has already been described in the subsection regarding the COT synthesis and is also reported in a previously published work.[136] It starts with a SET generating a radical that couples intermolecularly with another indole group and is followed by an HAT that completes the homocoupling. In the following mechanism the presence of the indole is fundamental for both its electron density and its relatively stable iminium form. Indole is initially attacked on its C3 generating an iminium ion (**Scheme 2.7**, Step A). While the acid seems necessary to trigger the initial step, this event alone is not sufficient since protonation with strong acid would happen on all indole-based substrates.

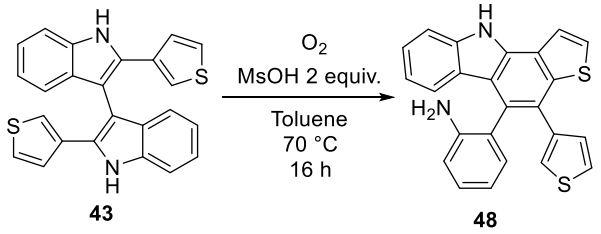
The high electrophilicity of the iminium ion promotes an intramolecular nucleophilic attack (Step B) but still requires a nucleophilic carbon to be close, making the nature of the substituent equivalently important. Deprotonation follows, giving rise to a relatively stable intermediate (Step C).

In the presence of oAC_{HNO3}, the SET that had previously generated **43** would take place again on the unreacted indole (Step D.1) producing a radical cation that would stabilize itself by homolytically losing a proton through HAT (Step E). The final rearrangement is promoted by a strong localization of positive charge next to the thiophene and by imine formation on the carbon where the thiophene initially was (Step F).



Scheme 2.7 Possible rearrangement mechanism with a secondary path for ring opening.

The neutral intermediate formed after Step C offers, however, another possible reaction pathway catalyzed by the acid. The possible protonation of the secondary amine may promote the aromatization of the newly formed 6-member ring, resulting in the opening of the previous indole (Step D.2) similarly to what was previously reported by G. Jacquemot *et al.*[148] This hypothetical pathway has been tested for **43** using conditions equal to the optimal ones for the synthesis of **41** but in the absence of oAC_{HNO3}. The outcome of this reaction was the almost quantitative synthesis of the expected product **48** (**Scheme 2.8**).



Scheme 2.8 Acid catalysed test reaction for an alternative reaction pathway.

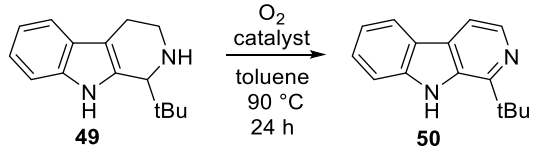
This acid test supports steps A, B and C, showing that acid is the main catalyst in the initial part of the mechanism. The supposed irreversibility of step D.2 and complete lack of **48** in other reactions supports a complete reversed selectivity toward step E when oAC_{HNO3} is present, resulting into an elegant concerted reaction.

2.3 - Aromatization of *N*-heterocycles

Since oACs have been proven to be able to catalyze oxidative dehydrogenations we decided to explore their potential for the aromatization of heterocycles, and to investigate their applicability for these processes, which are widely employed in research but also in the pharmaceutical industry.

2.3.1 - Screening and optimization

The reaction chosen as target for the catalyst screening was the dehydrogenative aromatization of 1-*tert*-butyl-1,2,3,4-tetrahydro-β-carboline. For this new process, all the oACs prepared were tested, as well as compared with pristine AC and oAC_{air} before decarboxylation.



49 **50**

Entry	Catalyst	Catalyst (equiv.)	Yield (%)
1	-	-	2
2	AC	4	34
3	oAC_{air}	4	57
4	$oAC_{air(\Delta)}$	4	59
5	oAC_{HNO3}	4	36
6	rGO	4	52
7	GO	2	1
8	oCNT	2	20
9	PQ	0.5	33 (22[a])
10	AQ	0.5	2
11	Tetracene	0.5	1

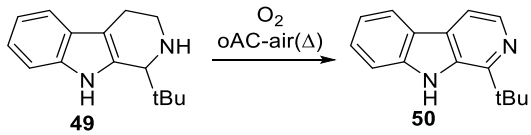
[a] Under Ar atmosphere.

Table 2.22 Catalyst screening of aromatization to β-carbolines.

HCl washed AC already delivered a yield of 34% (**Table 2.22**, entry 2), and every oxidative treatment improved the catalytic activity. Surprisingly, oAC_{HNO3} showed the smallest improvement, with an increase of only 2% in yield (entry 5). Air oxidized AC, before and after decarboxylation gave the best results respectively of 59% for $oAC_{air(\Delta)}$ (entry 4) and 57% for oAC_{air} (entry 3).

Other well-known carbocatalysts were tested as a comparison: GO showed almost no activity (entry 7) while rGO proved to be moderately active, delivering 52% of **50** (entry 6). Oxidized CNTs, which showed high activity for ODH couplings of aryls in a previous work by the group[140], in this case only provided 20% yield (entry 8).

As we observed for the indole coupling reaction, we hypothesized that the carboxylic/quinone groups would be the main active site involved in this reaction's catalytic promotion. For this reason, molecular quinones were employed as molecular models: for this reaction, AQ showed no activity (2% yield, entry 10) while PQ revealed a moderate yield under Ar (22%), which improved under O_2 atmosphere (33%, entry 9). Previously, tetracene has been used to mimic the zig-zag edges of the carbon materials' graphitic portion, which have been reported to be another possible catalytic active site[149], but in this case no activity was detected (1%, entry 11).



49 **50**

Entry	Catalyst (equiv.)	*T*(°C)	Time (h)	Yield (%)
1	4	90	24	59
2	1	90	24	30
3	2	90	24	42
4	4	90	3	44
5	4	90	72	67
6	4	25	24	26
7	4	140	24	67
8	4	90	24	24[a]
9	4	90	24	22[b]

[a] Under Ar atmosphere. [b] With 1 equiv. MsOH.

Table 2.23 Optimization of aromatization to β-carbolines.

Variations of the catalyst loading suggested that quite high loadings are needed: the best result was obtained with 4 weight equivalents of $oAC_{air(\Delta)}$ (**Table 2.23**, entries 1, 2 and 3), which was the highest possible amount to ensure proper stirring of the mixture. While a short reaction time reaction test showed that most of the conversion occurs in the first 3 h (entry 4) the optimal time to achieve the highest yield in the same conditions was revealed to be 72 h (entry 5). An increase of the temperature to 140 °C has proven to be beneficial as well, producing the same yield but in just 24 h (entry 7). In this case, anisole was chosen as solvent, both for its higher boiling point and for its good environmental profile.

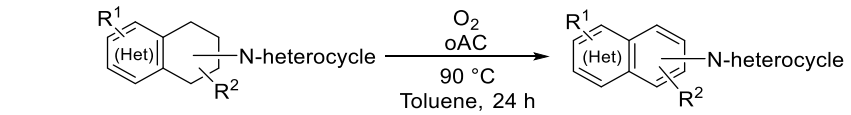
The role of oxygen as terminal oxidant in this reaction was confirmed by testing the reaction at 90 °C for 24 h under Ar atmosphere. The obtained lowered yield of 24% confirms the importance of oxygen in regenerating the catalytic active sites.

The MsOH additive, which was crucial for COTs synthesis, was tested in this case as well. A critical decrease of activity, obtaining only 22% yield, was however obtained. This observation suggests that a different mechanism is at play, which does not benefit by the presence of acids. This also suggests a hypothesis on why oAC_{HNO3} is not as effective for this reaction as it was for the previously studied couplings: the

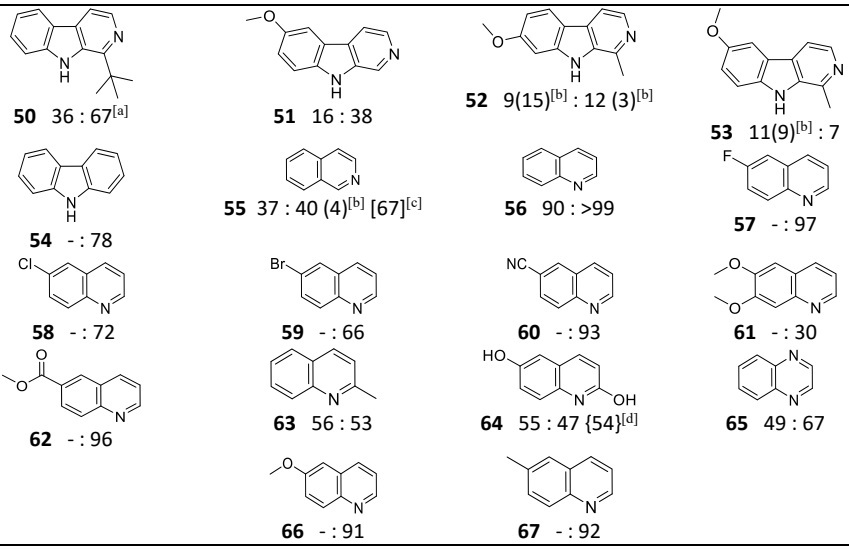
abundance of carboxylic acid groups is more detrimental than beneficial in this case. The superior activity of the $oAC_{air(\Delta)}$ compared to oAC_{HNO3} observed has an additional benefit, as the production protocol is more environmentally friendly.

2.3.2 - Reaction scope

After establishing the optimized reaction conditions, we studied the scope of ODH aromatizations with other partially unsaturated heteroaryls. Both catalysts were tested for all reactions as the activation mechanism might be different.



Yield (%)
oAC_{HNO3} : $oAC_{air(\Delta)}$



50 36 : 67[a]
51 16 : 38
52 9(15)[b] : 12 (3)[b]
53 11(9)[b] : 7
54 - : 78
55 37 : 40 (4)[b] [67][c]
56 90 : >99
57 - : 97
58 - : 72
59 - : 66
60 - : 93
61 - : 30
62 - : 96
63 56 : 53
64 55 : 47 {54}[d]
65 49 : 67
66 - : 91
67 - : 92

[a] reaction time: 72 h. [b] 3,4-dihydro intermediate. [c] reaction at 100 °C, 72 h. [d] 140 °C, 72 h.

Table 2.24 Aromatization of various substrates.

The study on β-carbolines was continued with the family of harmala alkaloids (**Table 2.24**). The addition of methoxy group at C6 and removal of tBu from C1 resulted in a moderate decrease in yield (**51**), which became more accentuated when a methyl group was added on C1 as in case of harmine (**52**, 12%) and isoharmine (**53**, 7%). For these substrates, partially aromatized intermediates were isolated and characterized as well.

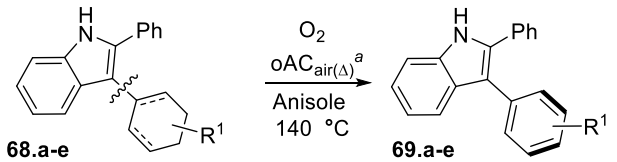
The synthesis of quinolines and isoquinolines was also been studied, starting from 1,2,3,4-tetrahydro intermediates. Unsubstituted or monosubstituted quinolines

have all been obtained in excellent to quantitative yields with the exception of 6-chloro (**58**, 72%), 6-bromo (**59**, 66%) and quinaldine (**63**, 56%). 1,2,3,4-tetrahydro-quinoxaline (**65**, 67%) showed lower reactivity than 1,2,3,4-tetrahydro-quinoline, and isoquinoline in the same conditions, was obtained in even lower yield (**55**). In this last case, the yield could be improved to 67% by increasing the temperature to 100 °C and running the reaction for 72 h.

The comparison between catalysts has proven $oAC_{air(\Delta)}$ to be better for most of the substrates with the exception of quinaldine and 2,6-dihydroxyquinoline (**64**, 55%), for which oAC_{HNO3} showed slightly better activity.

2.3.3 - ODH of tetrahydroaryl indoles

The dehydrogenation of a cyclic olefin without heteroatoms was also tested with $oAC_{air(\Delta)}$. The substrate chosen was a 3-substituted 2-phenyl-indole (**Table 2.25**).



68.a-e **69.a-e**

R^1 = H, Me, OMe or CF_3

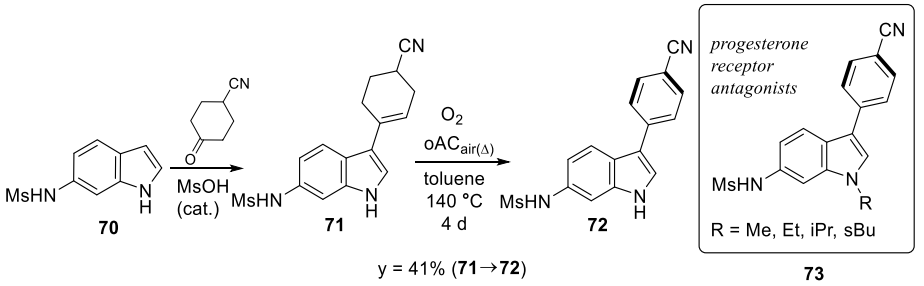
Entry	Substrate	Time (h)	Yield (%)
1	**a**	24	61
2	**b**	72	49
3	Me **c**	72	52
4	OMe **d**	24	Traces (69 **69.a**)
5	Me **e**	24	72
6	CF_3 **f**	24	65

Table 2.25 Aromatization of the olefinic ring.

The lower reactivity of these substrates forced us to employ more vigorous conditions, using anisole as solvent at 140 °C to speed up the reaction. Anyhow, some substrates (**69.b**, **69.c**) still required 3 days to react, achieving however moderate to good yields. With substrates having the olefinic ring conjugated to the indole, the speed of the reaction decreased drastically, except in the case in which the group

was localized para to the indole-ring bond (**69.d**, .**e**, .**f**). The presence of a methoxy group (**d**), though, resulted in OMe cleavage, yielding product **69.a**.

The easy preparation of the starting material and the good results obtained with the carbocatalyzed aromatization suggested a new protocol to obtain biaryl compounds instead of the classic Pd-mediated Suzuki-Miyaura couplings from halide and boronic acid (or ester) functionalized aryls. In order to test the viability of the concept we decided to synthesize a precursor of the progesterone receptor antagonist.

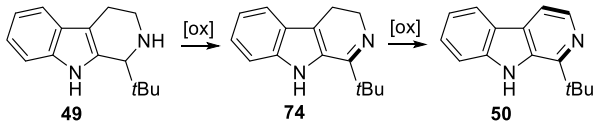


Scheme 2.9 Synthesis of a progesterone precursor.

The literature reported synthesis of this progesterone receptor antagonist begins with a 3-Br functionalized indole, which is then either converted to a boronic ester and coupled with aryl halide or coupled with a boronic ester aryl halide using Pd as catalyst[150]. The main downside of Pd couplings is that indole's NH is a very reactive group and it needs to be protected, which adds two additional steps to the synthetic protocol. We were able to carry out the synthesis of **72** from indole **70** and 4-oxocyclohexanecarbonitrile without purification of intermediate **71** in 2 steps with 41% yield without any pre-functionalization or N-protection (**Scheme 2.9**).

2.3.4 - Recyclability and kinetic

Kinetic monitoring of **50** with ^{1}H NMR, performed with both oAC_{HNO3} and $oAC_{air(\Delta)}$ shows that the aromatization reaction proceeds through a 3,4-dihydro intermediate (**Figure 2.9**).



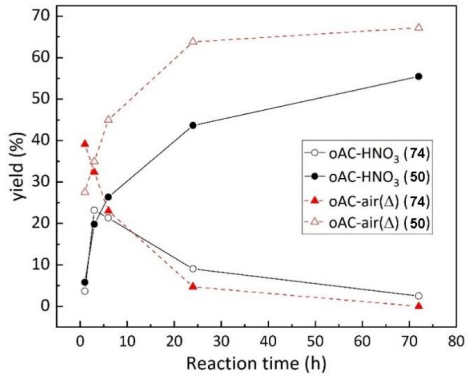


Figure 2.9 Kinetic monitoring of conversion of **49** to **50** via **74** (3,4-dihydrocarbazole) intermediate catalyzed by $oAC_{air(\Delta)}$ (red curve) and oAC_{HNO3} (black curve) at 90 °C.

Finally, the robustness and recyclability of the catalysts were investigated by performing recycling experiments. Six sequential cycles of ODH using the same substrate **49** as the starting material were run with both the oAC_{HNO3} and $oAC_{air(\Delta)}$. oACs were filtered off and thoroughly washed with CH_2Cl_2/MeOH (7%) between each cycle.

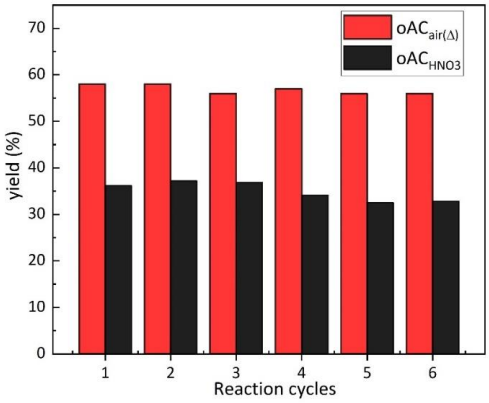
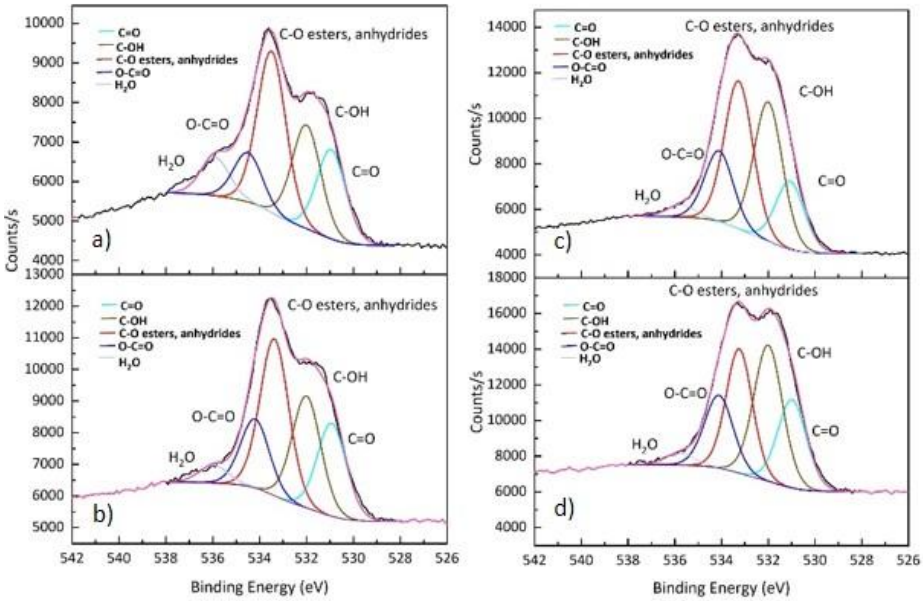


Figure 2.10 Catalysts' recyclability tests over 6 cycles in toluene with oAC_{HNO3} (black bars) and $oAC_{air(\Delta)}$ (red bars) for 24 h under O_2 at 90 °C. The yield was determined by 1H-NMR using 1,3,5-trimethoxybenzene as an external standard.

As reported in **Figure 2.10**, differently from the indole homocoupling reaction tested in our previous study[136], there isn't any drastic loss in activity throughout the 6 cycles, confirming the robustness and catalytic nature of the carbon materials. As a further proof of this statement, XPS of both carbocatalysts after recycling were recorded.



Material	H_2O	O-C=O	C-O esters, anhydrides	C-OH	C=O	N (pyrrolic)
Peak BE (eV)	535.9	524.2	533.3	532.3	531.1	400.33
oAC_{HNO3}	0.39	2.29	4.79	4.51	2.21	
oAC_{HNO3} recycled	0.34	2.09	3.27	3.91	2.53	3.19
$oAC_{air(\Delta)}$	0.73	0.93	3.04	1.95	1.69	
$oAC_{air(\Delta)}$ recycled	0.35	1.37	3.12	2.23	1.85	1.78

Table 2.25 Summary of oxygen and nitrogen 1s XPS peak deconvolutions for $oAC_{air(\Delta)}$ a) before and b) after, and oAC_{HNO3} c) before and d) after the recycling.

The O1s peaks' deconvolutions before and after catalysis are reported and summarized in Table 4. The peaks' deconvolution shows almost negligible variation in the oxygen groups' distribution in both cases. Notably, the appearance of a N 1s peak associated to pyrrolic nitrogen suggests a possible partial stoichiometric reaction with the substrate, which doesn't anyhow affect the activity of the catalyst.

2.4 - Conclusion and outlook

In the presented studies it was demonstrated that carbon-based materials rich in carbonyls and quinone moieties exhibit catalytical activity towards various ODH reactions. In this thesis framework, we analyzed the different catalytic activity of oAC_{HNO3} and $oAC_{air(\Delta)}$, similarly rich in active carbonylic and quinoidic moieties, but very different in other oxygen groups distribution and graphitic content, developing oxidized active carbon-based catalysts capable of catalyzing different organic oxidative reactions.

Although at first the catalytic activity seemed to be limited to *N*-heterocycles, the employment of acid additives allowed us to extend it to other heteroatom-bearing rings. In this fashion, we were able to tune the activity of the catalyst and arbitrarily choose to stop the reaction after the first coupling or make it proceed to the formation of the desired COT. This selectivity was proven to depend only on the acid addition when the substrate bore *N*-heterocycles, but when the substrate did not contain *N*-heterocycles also the distribution of the oxygen functionalities on the surface of the carbocatalyst played an important role.

This interesting interaction between acid additive and oAC's oxygen groups caused a divergence in selectivity that showed the possibility to direct the reaction towards an unexpected ring-cyclized partially dearomatized migration product with oAC_{HNO3}. The scope of this reaction was studied, and led to a hypothesized mechanism for the reaction.

Aromatization of *N*-heterocycles and 3-(cyclohexenyl)-indoles was achieved without any acid additive and with good recyclability and stability over six cycles with both oACs, confirming their robustness and catalytic behaviour. In this case $oAC_{air(\Delta)}$ offered improved efficiency compared to reported ACs with respect to *N*-heterocycle dehydrogenation and was employed to develop an alternative route for (hetero)biaryls, which can replace a multistep transition metal mediated sequence.

The metal-free carbon materials were proven to operate in catalytic fashion using O_2 as the terminal oxidant. The simple preparation and availability of the catalytic material, together with its good catalytic performance makes it a good competitor in the field of carbocatalysis.

Besides the development of the catalytic protocols, and knowing already the role of carbonyls as active sites, the most important point demonstrated by this thesis is the critical role of the other oxygen groups in determining selectivity and enhancing the catalytic activity, supporting the idea that further optimization of each reaction could be obtained with an ideal distribution of oxygen groups on oAC.

3 - EXPERIMENTAL SECTION

All reactions with activated carbon (AC) were carried out in a Teflon capped Biotage vial equipped with a magnetic stirring bar and a balloon filled with oxygen was connected with needle in order to maintain the oxygen atmosphere. Reactions were monitored with thin layer chromatography (TLC) with SiO_2 on aluminum coated plates. Mixtures of EtOAc and n-hexane (from 1:4 to 1:1) were used as eluents.

All oAC-catalysts were prepared from the same 1 kg batch (Lot. H2430) from Fluka with 100 mesh particle size. Catalytic activity of the oACs were defined with homocoupling reaction of 2-phenyl-indole (**Table 2.7**).

NMR yields were measured with a Bruker 500 MHz spectrometer using 1,3,5-trimethoxybenzene in DMSO-d_6 sealed in a capillary as an external standard and calibrated with various solutions of 1,3,5-trimethoxybenzene in DMSO-d_6. The crude products were dissolved in a measured amount of solvent and analyzed with proton spectra with the capillary inside. All other NMR spectra were recorded on Varian 300 MHz, Bruker 400 MHz, and Bruker 500 MHz spectrometers.

High resolution mass spectra (EI) were obtained on MS JEOL JMS-700.

The X-ray Photoelectron Spectroscopy (XPS) analysis was performed by Thermo Fisher Scientific ESCALAB 250Xi XPS System at the Center of Microscopy and Nanotechnology, University of Oulu (Finland). The monochromatic AlKα radiation (1486.7 eV) operated at 20 mA and 15 kV. The powder samples were put in gold sample holder and O, C, N and Au were measured for all samples. The measurement data were analyzed by Avantage V5 program developed by Thermo Fisher Scientific. Charge compensation was used to determine the presented spectra and the binding energies (BE) were calibrated by the C1s peak position of 284.8 eV. The deconvolution of the peaks was carried out for C1s and O1s with Avantage program utilizing peak BE values for groups as reported for carbon materials by Figueiredo and Pereira.[42]

3.1 - Carbon material treatments and procedures

Preparation of thermally air oxidized activated carbon, oAC_{air}

The active carbon was washed with dilute HCl to remove metal impurities. Activated carbon (16 g) and HCl (1 M, 128 ml) were loaded into a flask and the mixture was stirred in 70 °C for 17 h. The mixture was filtered in a Büchner funnel and washed with 3 L of deionized H_2O and dried in the oven at 140 °C for 16 h.

The carbon was then divided into four batches. Each individual batch (4 g) was then placed in a ceramic container and heated in an oven under static air atmosphere under the following conditions:

Temperature: 425 °C Heating rate: 14°C/min

Time (after reaching 425 °C): 16 h

Thermal treatment of air oxidized activated carbon, $oAC_{air(\Delta)}$[151]

The crucible was cooled down to r.t. and then heated in oven under Ar atmosphere, to decarboxylate oAC_{air} under the following conditions:

Temperature: 450 °C
Heating rate: 8 °C/min

Time (after reaching 450 °C): 24 h
Ar Flow: 20 mL/min

The resulting oAC was then cooled down to r.t. and stored into a vial.
Residual mass = 63-66%

Preparation HNO_3 oxidized activated carbon, oAC_{HNO3}

As above for the air oxidation, the AC was washed in same manner with dilute HCl to remove metal impurities. Each 4 g batch was loaded into a glass flask and conc. (70%) HNO_3 was added dropwise until a slurry was formed (8 mL).

After HNO_3 addition, the flask was attached with tube to a Dreschel bottle from which tubing lead the formed gas into a beaker filled with dilute NaOH (aq.). The flask was heated at 140 °C for 16 h and kept under vacuum at 140 °C for 2 h. Product was then cooled down to r.t.

Residual mass = 97%

Preparation NOx oxidized activated carbon, oAC_{NOx}

1 g of AC washed with HCl was loaded into a column with a frit and joined on the top with an airlock similar to the one used for oAC_{HNO3}, and on the bottom to a flask loaded with 10 g of Cu. 20 mL of HNO_3 70% was dropped in 2,5 h in this sealed flask and the carbon was kept there for further 2,5 h.

The resulting oAC was then kept cycled through vacuum-air 10 times to remove residual NOx.

General procedure of oxidative coupling without additive (GP 1)

Starting material and oAC catalyst (224 g/mol of SM) were loaded into a vial and toluene was added to reach 0.25 M solution of substrate. Vial was sealed with a septa cap. Reaction container was degassed with vacuum and refilled with O_2 (3 times) after which O_2 balloon was attached with a needle. The reaction mixture was stirred at 90 °C for 1.5-24 h. Reaction mixture was cooled in a water bath to r.t., filtered through celite and washed with DCM. Solvents were evaporated and the crude product(s) were purified through a column using silica as stationary phase and EtOAc:nHex as eluent.

General procedure of oxidative coupling with $MeSO_3H$ (GP 2)

Catalysis was performed as GP 1 with 1-5 equiv MsOH as additive. After the reaction was cooled down to r.t., it was filtered through basic alumina and celite with DCM, solvents were evaporated and the product(s) were purified through a column with silica as stationary phase and EtOAc:nHex as eluent.

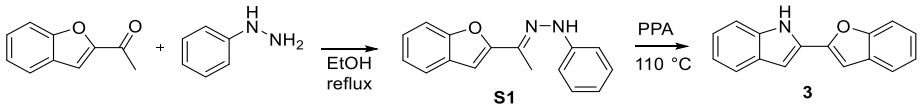
Standard procedure for analysis of oAC's catalytic activity

We used oxidative dehydrogenative homocoupling of commercially available 2-phenylindole as reference substrate was used to measure catalytic activity of carbon materials (**Table 2.7**).[136] Herein, the coupling reaction revealed that oAC_{HNO3} catalyst gave better yield (38%) in 1.5 h than $oAC_{air(\Delta)}$ (15%). Notably, the coupling yield could be improved with acid additives, of which MsOH gave the best yield (58%), but at the expense of selectivity that decreased from 73% to 58%.

The standard reaction conditions were as follow: GP1 with 2-phenylindole (19.4 mg, 0.10 mmol) in toluene (0.1 M) with 1 eq. of oAC and 1 eq. of the acid, when used.

3.2 - Synthesis

2-(benzofuran-2-yl)-1H-indole (3)[152]



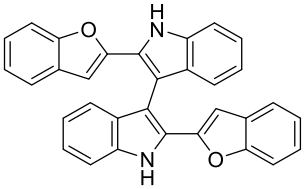
The synthesis of **3** was carried out in 2 steps:
(a) 2-acylbenzofuran (2 g, 12.5 mmol) was loaded into a dried flask connected to a dried Dean-Stark apparatus and dissolved in 50.5 ml of EtOH:AcOH (100:1). The solution was refluxed for 5 min to eliminate the water and then phenylhydrazine (1.25 mL, 12.7 mmol) was injected and refluxing was continued for 3 h. Solvents were evaporated and the residue was adsorbed in silica and purified with a flash column chromatography using EtOAc:nHex (1:9 -> 1:4) as eluent. Yield of **S1** was 2.60 g, 84%.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56 (1H, d), 7.52 (1H, d), 7.35-7.27 (2H, m), 7.25-7.18 (4H, m), 6.96 (1H, s), 6.92 (1H, t), 2.29 (3H, s).

(b) PPA (8.5 g) was loaded into a flask and preheated to 110 °C. **S1** (0.85 g, 3.40 mmol) was then added and the mixture was mechanically stirred for 1 h. The reaction mixture was cooled down to r.t., quenched with H_2O and neutralized with saturated Na_2CO_3 (aq.). Residual salts were washed from the crude product with an excess of water. Crude product was refluxed in DCM:nHex (1:1) to remove impurities from the solid product. Yield of **3** was 0.369 g, 47%. NMR matches literature[153].

^{1}H NMR (300 MHz, DMSO-*d*6) δ = 11.81 (1H, s), 7.70 (1H, d), 7.63 (1H, d), 7.60 (1H, d), 7.44 (1H, d), 7.33 (1H, t), 7.31 (1H, s), 7.28 (1H, t), 7.17 (1H, t), 7.05 (1H, t), 6.97 (1H, s).

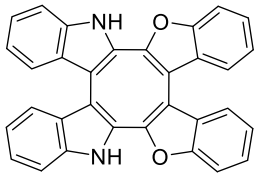
2,2'-di(benzofuran-2-yl)-1H,1'H-3,3'-biindole (4)



Compound **4** was prepared following the GP1 with **3** (29.8 mg, 0.13 mmol) and $oAC_{air(\Delta)}$ (28.2 mg) with 24 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9 ->1:2) as eluent. Yield of **4** was 22.3 mg, 75%.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 12.10 (s, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.26 – 7.18 (m, 4H), 7.15 – 7.08 (m, 4H), 6.95 (dd, *J* = 8.0, 6.9 Hz, 2H), 6.40 (d, *J* = 0.9 Hz, 2H).
^{13}C NMR (75 MHz, DMSO-d_6) δ = 153.33, 149.13, 136.71, 128.46, 128.36, 125.80, 124.36, 123.16, 122.86, 121.01, 119.73, 119.54, 112.03, 110.66, 107.09, 102.36.
HRMS Calculated for $[C_{32}H_{20}N_2O_2+]$: 464.1525, found: 464.1533

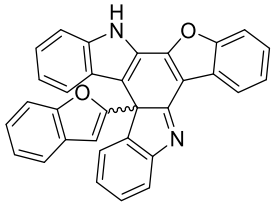
2-(benzofuran-2-yl)indole dimer COT (5)



Compound **5** was prepared following the GP2 with **3** (29.5 mg, 0.13 mmol), $oAC_{air(\Delta)}$ (140.1 mg) and MsOH (40.6 µL, 0.62 mmol) with 1.3 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **5** was 16.6 mg, 58%.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.95 (s, 2H), 7.75 (d, *J* = 8.9 Hz, 2H), 7.49 – 7.42 (m, 6H), 7.38 – 7.32 (m, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.23 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.07 (dd, *J* = 8.1, 7.0 Hz, 2H).
^{13}C NMR (75 MHz, DMSO) δ = 155.50, 146.86, 138.28, 127.03, 126.40, 125.58, 124.42, 123.57, 123.20, 120.98, 120.80, 119.63, 112.32, 112.08, 111.81, 111.78.
HRMS Calculated for $[C_{32}H_{18}N_2O_2+]$: 462.1368, found: 494.1377

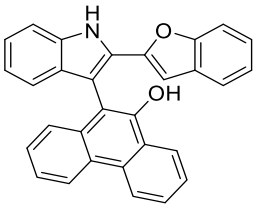
15b-(benzofuran-2-yl)-5,15b-dihydrobenzofuro[2,3-a]indolo[2,3-c]carbazole (6)



Compound **6** was prepared following the GP2 with **3** (11.9 mg, 51.0 µmol), $oAC_{air(\Delta)}$ (33.1 mg) and MsOH (9.7 µL, 0.15 mmol) with 5 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4 -> 1:9) as eluent. Yield of **6** was 9.3 mg, 79%.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.67 (s, 1H), 8.41 – 8.36 (m, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.82 – 7.75 (m, 2H), 7.57 – 7.50 (m, 2H), 7.50 – 7.45 (m, 2H), 7.41 (td, *J* = 7.5, 1.1 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 1H), 7.11 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.06 (td, *J* = 7.4, 1.1 Hz, 1H), 6.12 (d, *J* = 0.9 Hz, 1H).
^{13}C NMR (126 MHz, DMSO) δ = 175.93, 156.58, 156.54, 155.19, 154.18, 153.10, 137.60, 136.79, 129.38, 127.38, 126.19, 125.97, 125.87, 125.77, 125.14, 124.78, 124.31, 123.74, 123.60, 122.88, 121.30, 121.22, 121.12, 120.97, 120.26, 115.50, 112.97, 112.03, 110.86, 110.34, 102.25, 63.71.
HRMS Calculated for $[C_{32}H_{18}N_2O_2+]$: 462.1368, found: 462.1382

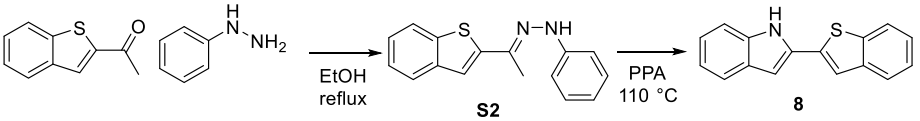
10-(2-(benzofuran-2-yl)-1H-indol-3-yl)phenanthren-9-ol (7)



Compound **7** was prepared analogously to GP2 procedure using **3** (29.5 mg, 0.13 mmol) as substrate, phenantrenequinone (27.1 mg, 0.13 mmol) instead of oAC, and MsOH (8.2 µL, 0.13 mmol). Reaction time was 20 h. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:12->1:9) as eluent. Yield of **7** was 1.5 mg, 3%.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.14 (s, 1H), 8.94 (s, 1H), 8.93 (d, *J* = 8.3 Hz, 1H), 8.83 (d, *J* = 7.6 Hz, 1H), 8.40 (d, *J* = 8.3 Hz, 1H), 7.80 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.73 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 6.8, 6.8 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.31 (dd, *J* = 6.9, 6.8 Hz, 1H), 7.28 – 7.18 (m, 3H), 7.11 (dd, *J* = 7.5 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.23 (s, 1H).
^{13}C NMR (126 MHz, DMSO-d_6) δ = 153.28, 149.24, 149.02, 132.78, 130.93, 129.32, 128.55, 127.26, 127.11, 126.91, 126.55, 126.09, 125.82, 124.84, 124.38, 123.66, 123.19 (2C), 122.93 (2C), 121.03, 119.65, 119.29, 111.96, 110.69, 109.15, 107.87, 102.08.
HRMS Calculated for [$C_{30}H_{19}NO_2$+]: 425.1416, found: 425.1397

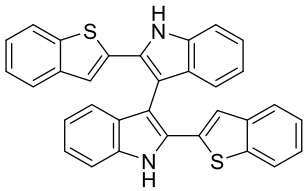
2-(benzo[b]thiophen-2-yl)-1H-indole (8)



The synthesis of 2-(benzo[b]thiophen-2-yl)-1H-indole was carried out in two steps as a one-pot sequence:
(a) 1-(benzo[b]thiophen-2-yl)ethan-1-one (1.506 g, 8.5 mmol) and phenyl-hydrazine (0.85 mL, 8.7 mmol) were dissolved in EtOH abs. (50 mL) and heated up to reflux in a dean-stark system, every 30 minutes the 10 mL EtOH accumulated were substituted with new EtOH absolute. The reaction was refluxed for 23 h. After evaporating the solvents in a rotary evaporator the crude product was broken in small chunks. **S2** was used for the next step without purification.
(b) PPA (25.2 g) was added to the crude product and mixture was heated to 110 °C, the mixture was stirred mechanically for 1 h. The reaction was then cooled down, quenched with H_2O and neutralized with $NaHCO_3$ (aq.) sature. The precipitate was filtered, washed with H_2O and the product was extracted with DCM. Product was purified by recrystallization with DCM and n-hexane. Yield of **8** was 1.18 g, 55%. NMR match literature[153].

^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.77 (s, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 7.3 Hz, 1H), 7.81 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.43 – 7.33 (m, 3H), 7.15 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H).

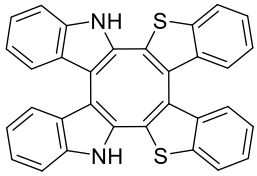
2,2'-bis(benzo[b]thiophen-2-yl)-1H,1'H-3,3'-biindole (9)



Compound **9** was prepared following the GP2 at 70 °C with **8** (62.2 mg, 0.25 mmol), $oAC_{air(\Delta)}$ (56.0 mg) and MsOH (8.0 µL, 0.12 mmol) with 24 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **9** was 52.8 mg, 85%.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.00 (s, 2H), 7.86 (s, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.26 (dd, 2H), 7.21 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.16 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.93 (dd, *J* = 7.4 Hz, 2H).
^{13}C NMR (75 MHz, DMSO) δ = 139.22, 138.77, 136.99, 134.72, 131.27, 129.52, 124.46, 124.22, 123.14, 122.84, 121.98, 119.75, 119.64, 119.16, 111.31, 106.71
HRMS Calculated for [$C_{32}H_{20}S_2O_2$+]: 496.1068, found: 496.1071

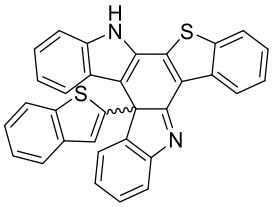
2-(benzo[b]thiophen-2-yl)indole dimer COT (10)



Compound **10** was prepared following the GP2 with **8** (62.7 mg, 0.25 mmol), $oAC_{air(\Delta)}$ (281.5 mg) and MsOH (32.6 µL, 0.50 mmol) with 6 h reaction time. Product was purified using flash column chromatography with silica as fixed phase and EtOAc:nHex (1:4) as eluent. Yield of **10** was 1.4 mg, 2%.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.81 (s, 2H), 8.11 (d, J = 8.1 Hz, 2H), 7.44 (m, 4H), 7.38 (d, J = 8.0, 2H), 7.33 (dd, J = 8.2, 7.2, 2H), 7.20 (dd, J= 8.2, 7.0, 2H), 7.1 (d, J= 8.1, 2H), 7.05 (dd, J= 8.0, 7.0, 2H).
^{13}C NMR (75 MHz, DMSO-d_6) δ = 140.01, 138.01, 137.73, 134.34, 130.15, 128.40, 126.84, 125.14, 124.72, 124.44, 122.98, 122.76, 120.51, 119.63, 111.93, 110.87.
HRMS Calculated for [$C_{32}H_{18}S_2O_2$+]: 494.0911, found: 494.0899

15b-(benzo[b]thiophen-2-yl)-5,15b-dihydrobenzo[4,5]thieno[2,3-a]indolo[2,3-c]carbazole (11)



Compound **11** was prepared following the GP2 at 70 °C with **8** (63.5 mg, 0.25 mmol), $oAC_{air(\Delta)}$ (113.5 mg) and MsOH (33.1 µL, 0.51 mmol) with 16 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **11** was 25.8 mg, 41%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.45 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.36 (d, *J* = 7.4 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.59 – 7.52 (m, 4H), 7.49 – 7.44 (m, 2H), 7.28 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.21 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.19 – 7.12 (m, 2H), 6.67 (d, *J* = 0.7 Hz, 1H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 178.81, 155.85, 146.53, 139.54, 138.67, 138.50, 138.30, 137.84, 137.45, 135.56, 129.80, 129.36, 126.69, 126.14, 126.08, 125.66, 125.56, 124.28, 124.26, 124.12, 123.37 (3C), 123.34, 122.09, 121.67, 121.06, 120.03 (2C), 114.93, 112.63, 64.55.

^{1}H NMR (500 MHz, Acetone-d_6) δ = 11.36 (s, 1H), 8.52 (d, *J* = 7.9 Hz, 1H), 8.41 (d, *J* = 7.7 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.55 (dtd, *J* = 12.0, 7.9, 1.1 Hz, 3H), 7.51 - 7.42 (m, 3H), 7.28 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.23 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.74 (d, *J* = 0.8 Hz, 1H).
^{13}C NMR (126 MHz, Acetone- d_6) δ = 180.08, 157.61, 148.01, 141.07, 140.20, 140.07, 139.82, 138.75, 138.55, 137.24, 131.20, 130.13, 127.37, 127.29, 127.13, 126.79, 126.40, 125.98, 125.04, 125.03, 124.83, 124.42, 124.10, 123.74, 122.75, 122.73, 122.06, 121.37, 121.26, 116.92, 113.38, 66.15.
HRMS Calculated for [$C_{32}H_{18}S_2N_2$+]: 494.0911; found: 494.0893

Crystal Structure Determination of 11

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with PhotonII at 123(2) K using Cu-Kα radiation (*λ* = 1.54178 Å). Dual space methods (SHELXT for **11**) [G. M. Sheldrick, *Acta Crystallogr.* 2015, **A71**, 3-8] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2)[154]. H(N) hydrogen atoms were localized by difference electron density determination and all hydrogen atoms refined using a riding model. A semi-empirical absorption correction was applied. The structure is refined as a pseudo-merohedral two component twin. The solvent molecules and the benzo[b]thiopehn-2-yl moiety are disordered. Due to the bad quality of the structure, only the constitution and conformation were determined and the data were not deposited in the Cambridge Database.

11: yellow crystals, $C_{32}H_{18}N_2S_2 \cdot C_2H_6OS$, M_r = 572.73, crystal size 0.20 × 0.10 × 0.06 mm, monoclinic, space group $P2_1/n$ (No. 14), *a* = 15.4795(4) Å, *b* = 10.1733(3) Å, *c* =

35.6140(10) Å, β = 102.479(1)°, V = 5475.9(3) Å^3, Z = 8, ρ = 1.389 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 272 mm^{-1}, F(000) = 2384, $2\theta_{max}$ = 144.4°, 89369 reflections, of which 11077 (10621 observed, I > 2σ(I)) were independent (R_{int} = 0.035).

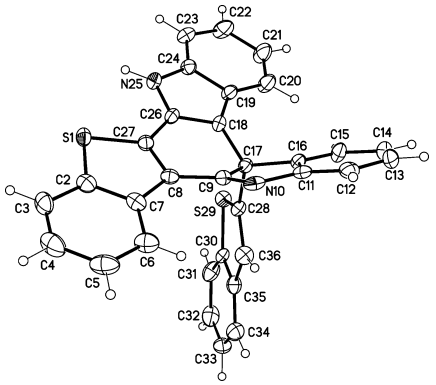
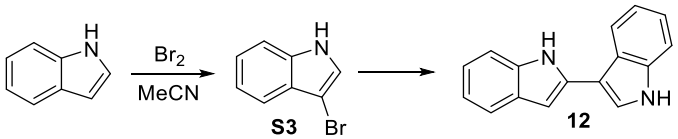


Figure S1 Molecular structure of one of the two crystallographic independent molecules of **11** (minor disordered part omitted for clarity, displacement parameters are drawn at 50 % probability level).

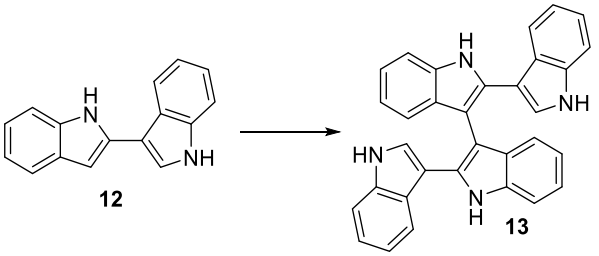
1H,1'H-2,3'-biindole (12)[155]



Indole (2.3454 g, 20.0 mmol) was loaded into a flask and dissolved in MeCN (30 mL). Solution is cooled to 0°C and stirred magnetically before adding Br_2 (0.55 mL, 10.7 mmol) dropwise in 20'. After 16 h solution is neutralized with K_2CO_3 10% (aq) and product was extracted with DCM. Colored impurities are removed by passing the organic solution through a short column, solvent is then evaporated and crude product is purified through recrystallization on DCM:nHex 1:1. Yield of **12** was 1.94 g, 84%. NMR match literature.[156]

^{1}H NMR (300 MHz, DMSO) δ 11.37 (s, 1H), 11.17 (s, 1H), 8.00 (dd, J = 6.8, 1.9 Hz, 1H), 7.86 (d, J = 2.6 Hz, 1H), 7.55 – 7.42 (m, 2H), 7.35 (dd, J = 7.8, 1.1 Hz, 1H), 7.25 – 7.09 (m, 2H), 7.09 – 6.90 (m, 2H), 6.75 (dd, J = 2.1, 0.8 Hz, 1H).

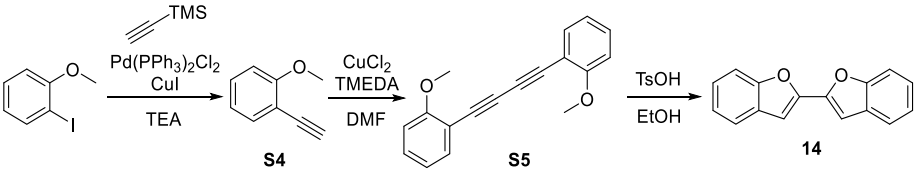
1H,1'H,1''H,1'''H-3,2':3',3'':2'',3'''-quaterindole (13)



Compound **13** was prepared following the GP1 with **12** (63.4 mg, 0.27 mmol) and $oAC_{air(\Delta)}$ (60.3 mg) with 4 h reaction time. Product was purified using flash column chromatography with silica as fixed phase and EtOAc:nHex (1:4) as eluent. Yield of **13** was 54.3 mg, 87%.

^{1}H NMR (500 MHz, DMSO) δ 11.13 (s, 2H), 11.05 (s, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.13 (s, 2H), 7.05 (t, J = 7.6 Hz, 2H), 6.98 (d, J = 7.3 Hz, 2H), 6.95 (d, J = 7.4 Hz, 2H), 6.94 – 6.89 (m, 2H), 6.76 (t, J = 7.5 Hz, 2H).
^{13}C NMR (126 MHz, DMSO) δ 136.26, 135.85, 132.20, 129.75, 125.29, 124.25, 121.26, 120.09, 120.04, 119.11, 118.54, 118.45, 111.48, 110.96, 108.48, 104.97.
HRMS Calculated for [$C_{32}H_{22}N_4$+]: 462.1844; found: 462.1855

2,2'-bibenzofuran (14)[157]



The synthesis of **14** has been carried out in 3 steps:
(a)[158] $Pd(PPh_3)_2Cl_2$ (59.9 mg, 85.3 μmol) and CuI (28.5 mg, 0.149 mmol) were loaded in to a dry flask and dissolved in dry TEA, flask was degassed and refilled with Ar (3x). 2-iodo-anisole (1 mL, 7.69 mmol) and trimethylsilyl-acetylene (1.2 mL, 8.43 mmol) were added and the reaction was stirred at r.t. for 19 h. The reaction was quenched with EtOAc and filtered through celite and washed with EtOAc. The solvents were evaporated approximately to 5 mL volume. MeOH (100 mL) and 3 spoons of K_2CO_3 were added and the solution was stirred for 1 h. Reaction mixture was filtered through celite pad and washed with EtOAc and the product was separated with flash column chromatography using EtOAc:nHex (1:40) as eluent. Yield of **S4** was 0.846 g, 83%.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47 (dd, J = 7.4, 1.5 Hz, 1H), 7.33 (dd, J = 8.4, 7.5, 1H), 6.95 – 6.86 (m, 2H), 3.91 (s, 3H), 3.30 (s, 1H).

(b)[159][160] Compound **S4** (0.833 g, 6.30 mmol) and TMEDA (0.95 mL, 6.34 mmol) were mixed in dry DMF (12 mL) and injected in to a dry flask under Ar, the solution was degassed by bubbling Ar for 15 min. $CuCl_2$ (0.430 g, 3.20 mmol) was added and the

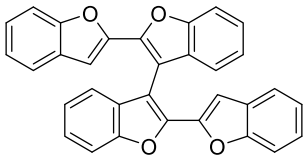
solution was stirred at 40 °C for 19 h. The reaction was quenched with H_2O and crude product was extracted with EtOAc. The organic phase was dried with $MgSO_4$ and solvent was evaporated. Product was purified with flash column chromatography using EtOAc:nHex (1:4) as eluent. Yield of **S5** was 0.610 g, 74%.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.48 (d, J = 7.6, 2H), 7.32 (dd, J = 8.4, 7.4, 2H), 6.91 (dd, J = 8.3, 7.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 3.90 (s, 6H).

(c) **S5** (0.61 g, 2.33 mmol) and TsOH (0.41g, 2.38 mmol) were loaded into a MW vial with EtOH (20 mL) and the vial was sealed. Reaction was carried out in a MW oven for 2 h at 160 °C. Once the reaction was completed, the vial was cooled to r.t. and let crystallize overnight in a freezer. The reaction mixture was filtered and the solid was dissolved in DCM and purified with flash column chromatography using DCM:nHex (1:1) as eluent. Yield of **14** was 0.283 g, 52%. NMR matches with literature.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.63 (d, J = 7.4, 2H), 7.55 (d, J = 8.4, 2H), 7.33 (dd, J = 8.2, 7.2 Hz, 2H), 7.27 (dd, J = 7.4, 1.2 Hz, 2H), 7.16 (d, J = 0.9 Hz, 2H).

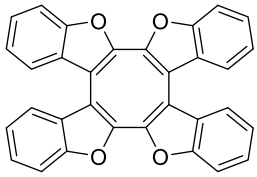
2,2':3',3'':2'',2'''-quaterbenzofuran (15)



Compound **15** was prepared following the GP2 at 70 °C with **14** (63.9 mg, 0.27 mmol), $oAC_{air(\Delta)}$ (285.8 mg) and MsOH (82.8 µL, 0.13 mmol) with 24 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:40) as eluent. Yield of **15** was 21.1 mg, 33%.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.4 Hz, 2H), 7.46 – 7.40 (m, 4H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.24 – 7.18 (m, 4H), 7.14 (t, *J* = 7.5 Hz, 2H), 6.90 (s, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.02, 154.82, 146.97, 144.84, 128.98, 128.27, 125.84, 125.28, 123.65, 123.38, 121.44, 121.22, 111.76, 111.48, 108.85, 106.05.
HRMS Calculated for [$C_{32}H_{18}O_4$+]: 466.1205, found: 466.1196

Tetrabenzofuran COT (16)

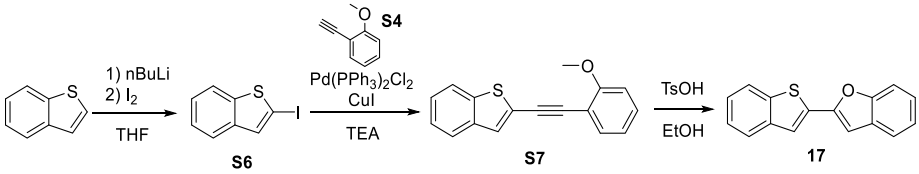


Compound **16** was prepared following the GP2 at 70 °C with **14** (44.5 mg, 0.19 mmol), oAC_{HNO3} (226.0 mg) and MsOH (61.7 µL, 0.95 mmol) with 17 h reaction time. Product

was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:40) as eluent. Yield of **16** was 9.8 mg, 22%.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.43 (dd, *J* = 8.5, 7.2 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.00, 143.38, 127.33, 126.36, 123.61, 122.06, 115.63, 112.23.
HRMS Calculated for [$C_{32}H_{16}O_4$+]: 464.1049, found: 464.1068

2-(benzo[b]thiophen-2-yl)benzofuran (17) [157]



The synthesis of **17** was carried out in 3 steps:
(a)[3] Benzothiophene (2.53 g, 18.9 mmol) was loaded into a dry flask and dissolved into dry THF (40 mL) under argon. The solution was cooled to –84 °C and nBuLi 1.6 M (13 mL, 20.8 mmol) was injected dropwise to the solution. After stirring the reaction for 10 min, a solution of I_2 (5.29 g, 20.8 mmol) in dry THF (50 mL) was added dropwise through a cannula and the resulting reaction mixture was stirred for 1 h. Then the mixture was let to warm up to r.t., quenched with NH_4Cl (aq.) and kept in the fridge overnight. Solid precipitate was filtered. Yield of **S6** was 4.86 g, 99%.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (1H, d), 7.71 (1H, d), 7.54 (1H, s), 7.32-7.26 (2H, m)

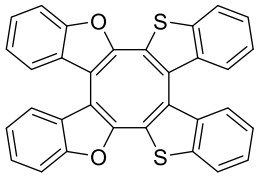
(b) Compounds **S6**, **S4** and 1-ethynyl-2-methoxybenzene (1.08 g, 4.2 mmol) were loaded into a dry flask with $Pd(PPh_3)_2Cl_2$ (37.2 mg, 1.3 mol%) and CuI (20.2 mg, 2.6 mol%), the flask was then degassed and refilled with Ar in three degas-refill cycles. Dry and degassed TEA was injected (20 mL) and the reaction was stirred for 19 h. EtOAc was added to the reaction mixture and the mixture was washed with saturated NH_4Cl (aq.) (3 times). The organic phase was dried with $MgSO_4$ and solvents were evaporated. Product was purified by flash column chromatography with DCM:nHex (1:4) as eluent. Yield of **S7** was 0.83 g, 76%.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.81-7.73 (m, 2H), 7.54-7.50 (m, 2H), 7.39-7.31 (m, 3H), 6.69 (t, 1H), 6.62 (d, 1H), 3.94 (s, 3H).

(c) Compound **S7** (0.83 g, 3.14 mmol) was loaded into a dry vial. Absolute EtOH (20 mL) and anhydrous TsOH (0.54 g, 3.16 mmol) were added to the vial. The vial was then sealed and the reaction was heated in a MW oven for 2 h at 160 °C after which the sealed vial was kept in fridge overnight. The precipitate was filtered, dissolved in DCM and purified with flash column chromatography using DCM as eluent. Yield of **17** was 0.60 g, 76%. NMR matches with literature.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.87-7.79 (m, 2H), 7.73 (s, 1H), 7.59 (d, 1H), 7.53 (d, 1H), 7.39-7.22 (m, 4H), 7.00(s, 1H)

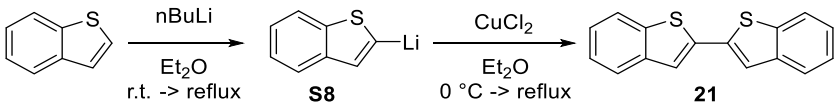
2-(benzo[b]thiophen-2-yl)benzofuran dimer COT (20)



Compound **20** was prepared following the GP2 with **17** (63.6 mg, 0.25 mmol), oAC_{HNO3} (286.0 mg) and MsOH (82.5 µL, 1.3 mmol) with 24 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:40) as eluent. Yield of **20** was 22.4 mg, 35%.

^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.94 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.37 (m, 4H), 7.33 – 7.21 (m, 6H).
^{13}C NMR (126 MHz, CD_2Cl_2) δ = 156.80, 148.01, 142.15, 138.87, 132.95, 131.88, 128.19, 126.29, 126.21, 125.37, 125.01, 123.89, 123.11, 122.09, 114.61, 112.29.
HRMS Calculated for [$C_{32}H_{16}S_2O_2$+]: 496.0592, found: 496.0578

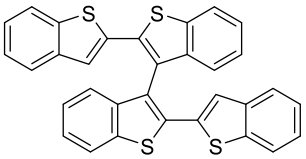
2,2'-bibenzo[b]thiophene (21)[161]



The synthesis of **21** has been carried out in 2-steps as a one-pot sequence:
$CuCl_2$ was previously kept at 140 °C under vacuum for 30 min for drying. Benzothiophene (0.7798 g, 5.81 mmol) was loaded into a dry flask and the flask was then degassed and refilled with Ar (2x). Dry Et_2O (29 mL) was injected into the flask and nBuLi 1.6M in n-Hexane (4.4 mL, 7.04 mmol) was added dropwise into the flask. After 5 min the solution was heated to 60 °C (reflux). After 2 h the reaction was cooled down to 0 °C and $CuCl_2$ (0.919 g, 6.84 mmol) was added to the reaction. The reaction mixture was then refluxed for 19 h. The reaction was cooled down to r.t. and precipitate was filtered through a short silica pad and washed with Et_2O. Any dissolved Cu was extracted with 2M HCl (aq.), organic phase was dried with $MgSO_4$ and solvents were evaporated, crude product was recrystallization from toluene. Yield of **21** was 0.144 g, 19%. NMR matches with literature.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 7.6 Hz, 2H), 7.77 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.52 (s, 2H), 7.35 (m, 4H).

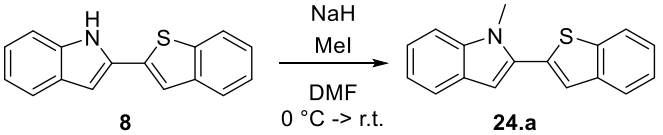
2,2':3',3'':2'',2'''-quaterbenzothiophene (22)



Compound **22** was prepared following the GP2 with **21** (33.8 mg, 0.13 mmol), $oAC_{air(\Delta)}$ (93.3 mg) and MsOH (24.7 µL, 0.38 mmol) with 5 h reaction time. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:30) as eluent. Yield of **22** was 12.6 mg, 37%.

^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.98 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.57 (s, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.43 – 7.38 (m, 2H), 7.28 – 7.22 (m, 6H), 7.19 (t, *J* = 8.2 Hz, 2H).
^{13}C NMR (126 MHz, CD_2Cl_2) δ = 141.24, 141.05, 139.57, 139.16, 137.96, 136.19, 126.97, 126.27, 125.65, 125.45, 125.15, 124.19, 123.69, 123.55, 122.75, 122.48.
HRMS Calculated for [$C_{32}H_{18}S_4$+]: 530.0291, found: 530.0295

2-(benzo[b]thiophen-2-yl)-1-methyl-1H-indole (24.a)[162]

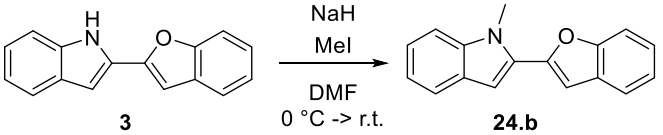


8 **24.a**

Compound **8** (0.36 g, 1.44 mmol) was loaded into a dry flask and is dissolved in dry DMF (25 mL), the solution is cooled down to 0 °C and NaH 60% (124.8 mg, 3.12 mmol) was added under slow magnetical stirring. After 25 minutes MeI (0.61 g, 4.3 mmol) was added and reaction was let heating up overnight. Reaction was quenched with NH_4Cl(aq) and filtered through a Buchner funnel, more water was added to quenched solution to make more produce precipitate. Product was finally dried under vacuum for 2 days. Yield of **24.a** was 0.38g, 99%.

^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.02 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.77 (d, J= 0.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.56 (dd, J = 8.3, 0.9, 1H), 7.47 – 7.37 (m, 2H), 7.24 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H) , 7.10 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.81 (d, J = 0.9 Hz, 1H), 3.97 (s, 3H).

2-(benzofuran-2-yl)-1-methyl-1H-indole (24.b)[162]



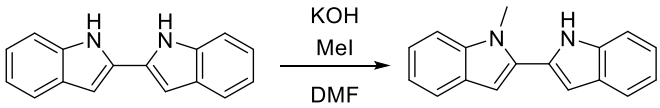
3 **24.b**

Compound **3** (0.12 g, 0.51 mmol) was loaded into a dry flask and is dissolved in dry DMF (10 mL), the solution is cooled down to 0 °C and NaH 60% (32.1 mg, 0.80 mmol) was added under slow magnetical stirring. After 34 minutes MeI (0.22 g, 1.5 mmol) was added and reaction was let heating up overnight. Reaction was quenched with NH_4Cl(aq) and filtered through a Buchner funnel, more water was added to quenched

solution to make more produce precipitate. Product was finally dried under vacuum for 2 days. Yield of **24.b** was 0.12g, 97%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 2H), 7.66 (dq, *J* = 8.1, 0.9 Hz, 2H), 7.63 (dt, J= 7.9, 1.0 Hz, 2H), 7.61-7.57 (m, 2H), 7.39 (d, J = 1.0, 2H), 7.41 – 7.32 (m, 2H), 7.30 (td, *J* = 7.4, 1.1 Hz, 2H) , 7.25 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 2H), 7.10 (ddd, J = 8.0, 7.0, 1.0 Hz, 2H), 7.04 (d, J = 0.8 Hz, 2H), 4.03 (s, 6H).

1-methyl-1H,1'H-2,2'-biindole (24.c)[163]

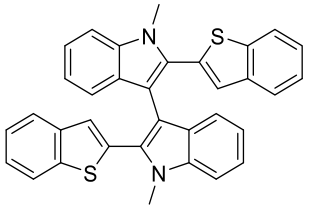


S9 **24.c**

Compound **S9** (0.29 g, 0.85 mmol) and KOH (176.0 mg, 3.13 mmol) were loaded into a dry flask and is dissolved in dry DMF (30 mL). MeI (0.120g, 8.45 mmol) was diluted in dry DMF (10 mL) and added dropwise, reaction was let stirring overnight. Reaction was quenched with EtOAc and filtered through a shot column with more EtOAc. Solvent was evaporated and crude product was separated through a column with EtOAc:nHex (1:9) as eluent. Yield of **24.c** was 61.1 mg, 29%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 7.64 – 7.58 (m, 2H), 7.55 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.43 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.21 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.88 (d, *J* = 0.8 Hz, 1H), 6.85 (dd, *J* = 2.2, 0.9 Hz, 1H), 3.98 (s, 3H).

2,2'-bis(benzo[b]thiophen-2-yl)-1,1'-dimethyl-1H,1'H-3,3'-biindole (25.a)



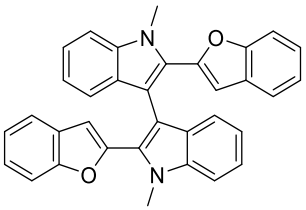
Compound **25.a** was prepared following the GP1 with **24.a** (65.8 mg, 0.25 mmol) and $oAC_{air(\Delta)}$ (57.1 mg) with 17 h reaction time. Product was filtered through celite with DCM and purified through recrystallization in DCM. Yield of **25.a** was 33.8 mg, 52%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (dd, *J* = 6.6, 0.9 Hz, 2H), 7.68 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.57 (dt, *J* = 8.3, 0.9 Hz, 2H), 7.35 – 7.25 (m, 6H), 7.23 – 7.16 (m, 4H), 6.95 (ddd, *J* = 7.9, 6.9, 0.9 Hz, 2H), 3.88 (s, 6H).

^{13}C NMR (101 MHz, DMSO) δ 139.97, 139.26, 137.57, 132.67, 131.61, 127.91, 124.85, 124.48, 124.29, 123.74, 122.46, 122.06, 119.74, 119.52, 110.36, 108.76, 31.35.

HRMS Calculated for [$C_{34}H_{24}N_2S_2$+]: 525.1414, found: 525.1395

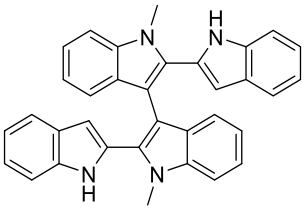
2,2'-di(benzofuran-2-yl)-1,1'-dimethyl-1H,1'H-3,3'-biindole (25.b)



Compound **25.b** was prepared following the GP1 with **24.b** (62.5 mg, 0.13 mmol) and $oAC_{air(\Delta)}$ (61.3 mg) with 17 h reaction time. Product was filtered through celite with DCM and purified through recrystallization in DCM. Yield of **25.b** was 21.6 mg, 35%.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 4H), 7.34 – 7.26 (m, 4H), 7.20 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.13 (dd, *J* = 7.3 Hz, 2H), 7.03 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 2H) , 6.43 (s, 2H), 4.05 (s, 6H).
^{13}C NMR (101 MHz, CD_2Cl_2) δ 155.23, 149.02, 138.82, 129.08, 128.95, 128.92, 124.76, 123.55, 123.33, 121.36, 120.92, 120.43, 111.50, 110.58, 110.19, 107.42, 32.61.
HRMS Calculated for $[C_{34}H_{24}N_2S_2+]$: 492.1838, found: 492.1824

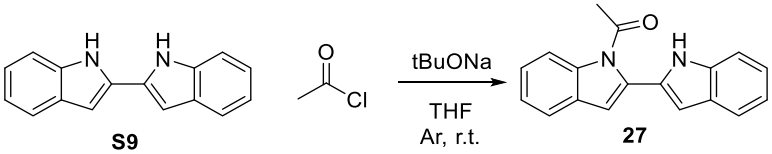
1',1''-dimethyl-1H,1'H,1''H,1'''H-2,2':3',3'':2'',2'''-quaterindole (25.c)



Compound **25.c** was prepared following the GP1 with **24.c** (61.1 mg, 0.25 mmol) and $oAC_{air(\Delta)}$ (55.6 mg) with 17h reaction time. Product was filtered through celite with DCM and purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9) as eluent. Yield of **25.c** was 22.1 mg, 36%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.12 (s, 2H), 7.50 (d, *J* = 7.4 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.16 – 7.02 (m, 6H), 6.95 (dd, *J* = 8.0, 7.0 Hz, 2H), 6.83 (dd, *J* = 7.9, 7.0 Hz, 2H), 6.32 (d, *J* = 2.1 Hz, 2H), 3.80 (s, 6H).
^{13}C NMR (75 MHz, DMSO-d_6) δ 137.15, 136.59, 131.36, 128.83, 127.96, 127.72, 121.79, 121.43, 120.04, 119.41, 119.16, 119.02, 111.29, 109.87, 108.41, 104.09, 31.24.
HRMS Calculated for $[C_{34}H_{26}N_4+]$: 490.2157, found: 490.2156

1-(1H,1'H-[2,2'-biindol]-1-yl)ethan-1-one (27)



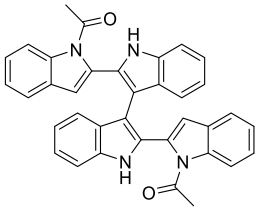
S9 **27**

Compound **S9** (0.13 g, 0.54 mmol) and tBuONa (56.0 mg, 0.58 mmol) were loaded in a dry flask under Ar and partially dissolved in dry THF (5 mL), and the solution was stirred magnetically. After 30 minutes acetyl chloride (0.10 g, 1.3 mmol) dissolved in

dry THF under Ar and was added dropwise via Teflon tube. After 1 h reaction was quenched in water and crude products were extracted with DCM. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9->1:4) as eluent. Yield of **27** was 11%.

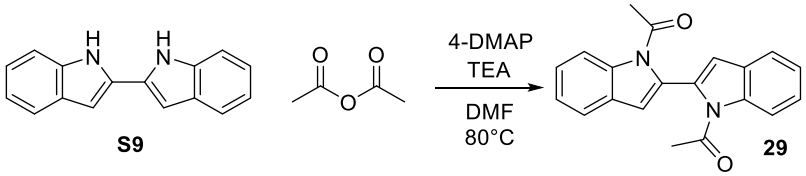
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.66 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.26 (m, 3H), 7.20 – 7.12 (m, 1H), 7.11 – 7.02 (m, 1H), 6.96 (d, *J* = 0.8 Hz, 1H), 6.75 (dd, *J* = 2.1, 0.9 Hz, 1H), 2.14 (s, 3H).

1,1'-(1H,1'H,1''H,1'''H-[2,2':3',3'':2'',2'''-quaterindole]-1,1'''-diyl)bis(ethan-1-one) (28)



Compound **28** was prepared following the GP1 with **27** (65.8 mg, 0.25 mmol) and $oAC_{air(\Delta)}$ (57.1 mg) with 21 h reaction time. Product was filtered through celite with DCM and purified through recrystallization in DCM. Yield of **28** was 33.8 mg, 52%.
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (s, 2H), 8.11 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 4H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.00 (s, 2H), 1.61 (s, 6H).
^{13}C NMR (126 MHz, DMSO) δ 169.74, 136.40, 136.14, 130.47, 128.07, 128.01, 126.88, 125.01, 123.25, 122.51, 120.36, 119.85, 119.63, 115.55, 112.52, 111.80, 108.92, 24.10.
HRMS Calculated for $[C_{36}H_{26}N_4O_2+]$: 546.2056, found: 546.2078

1,1'-(1H,1'H-[2,2'-biindole]-1,1'-diyl)bis(ethan-1-one) (29)

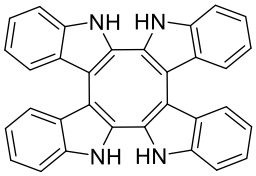


S9 **29**

Compound **S9** (0.33 g, 1.4 mmol) and 4-DMAP (15.7 mg, 0.14 mmol) were loaded in a dry flask under Ar atmosphere, and dry DMF(7 mL) and TEA (0.3 mL) distilled with CaH_2 were added. Acetic anhydride was added and the reaction heated up to 80°C in an oil bath. Reaction was kept in the dark and under magnetic stirring overnight. After 20 h the reaction was quenched with H_2O, products were extracted with EtOAc, the organic phase dried with $MgSO_4$ and evaporated completely in a rotavapor. The solid was dissolved partially in DCM and the mixture filtered in a Buchner funnel to remove unreacted **S9**, this process is repeated 2 times. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9->1:6) as eluent. Yield of **29** was 19%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (dq, *J* = 8.4, 0.9 Hz, 2H), 7.68 (ddd, *J* = 7.6, 1.5, 0.7 Hz, 2H), 7.42 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 2H), 7.33 (td, *J* = 7.5, 1.0 Hz, 2H), 6.95 (s, 2H), 2.38 (s, 6H).

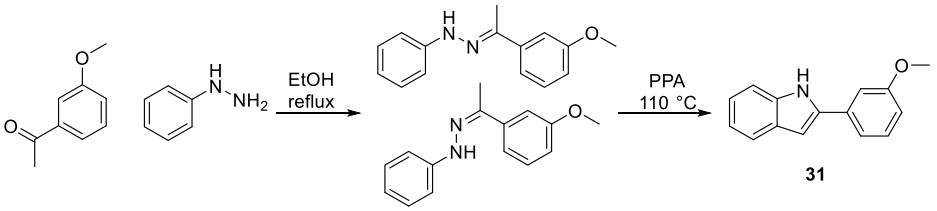
9,10,19,20-tetrahydrocycloocta[1,2-b:4,3-b':5,6-b'':8,7-b''']tetraindole (30)



Compound **30** was prepared following the GP1 with **29** (65.8 mg, 0.25 mmol) and oAC_{HNO3} (57.1 mg) with 17 h reaction time. Product was filtered through celite with DCM. Yield of **30** was 12%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (s, 4H), 7.43 (d, *J* = 8.1 Hz, 4H), 7.30 (d, *J* = 7.9 Hz, 4H), 7.15 (dd, *J* = 8.1, 7.0 Hz, 4H), 7.01 (dd, *J* = 8.0, 7.0 Hz, 4H).

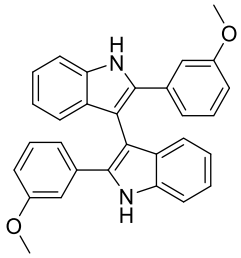
2-(3-methoxyphenyl)-1H-indole (31)



1-(3-Methoxyphenyl)ethanone (1.1 g, 7.3 mmol) and phenylhydrazine (0.72 mL, 7.3 mmol) were dissolved in EtOH abs. (60 mL) and heated up to reflux in a dean-stark system, and every 30 minutes the 10 mL EtOH accumulated was substituted with new EtOH absolute. After 1.5 h the solvent was evaporated in a rotavapor and kept under vacuum for 1 h. The crude intermediate solid product was then crushed into small pieces. PPA (20 mL) was added and the mixture was heated up to 110°C in an oil bath. The reaction was kept under mechanical stirring for 1 h before quenching with H_2O. The liquid phase was poured slowly in an Erlenmeyer flask with $NaHCO_3$ (aq.) sature and more $NaHCO_3$(aq) was used to clean completely the reaction flask and to completely neutralize the mixture. The solid precipitate was filtered, cleaned with H_2O and dried under vacuum. More product was extracted from the liquid phase with DCM, evaporated and kept under vacuum.
Product was recrystallized in DCM:nHex (1:1). Yield of **31** was 42%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H), 7.53 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.48 – 7.33 (m, 4H), 7.10 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.92 (dd, *J* = 2.2, 0.9 Hz, 1H), 6.88 (ddd, *J* = 8.1, 2.3, 1.2 Hz, 1H), 3.84 (s, 3H).

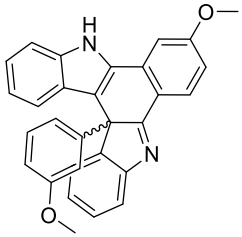
2,2'-bis(3-methoxyphenyl)-1H,1'H-3,3'-biindole (32)



Compound **32** was prepared following the GP1 with **31** (32.3 mg, 0.14 mmol) and oAC_{HNO3} (33.4 mg) with 30 h reaction time at 70 °C. Product was filtered through celite with DCM and purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **32** was 73%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.58 (s, 2H), 7.47 (dt, *J* = 8.1, 0.9 Hz, 2H), 7.18 – 7.07 (m, 8H), 6.94 (d, *J* = 7.5 Hz, 2H), 6.85 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 2H), 6.69 (ddd, *J* = 7.9, 2.6, 1.2 Hz, 2H), 3.44 (s, 6H).
^{13}C NMR (126 MHz, DMSO) δ 158.99, 136.35, 134.32, 134.01, 129.52, 129.39, 121.93, 119.25, 119.14, 118.50, 112.73, 111.54, 111.26, 106.57, 54.50.
HRMS Calculated for $[C_{30}H_{24}N_2O_2+]$: 444.1838, found: 444.1828

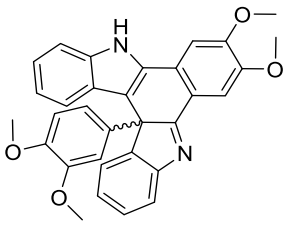
7-methoxy-14b-(3-methoxyphenyl)-5,14b-dihydrobenzo[a]indolo[2,3-c]carbazole (33)



Compound **33** was prepared analogously to GP2 procedure using **32** (57.1 mg, 0.26 mmol) as substrate, oAC_{HNO3} (117 mg) and *R*-camphorsulfonic acid (122 mg, 0.52 mmol) instead of $MeSO_3H$. Reaction time was 19 h and temperature was 70 °C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4->1:1) as eluent. Yield of **33** was 30.6 mg, 54%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 8.04 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.69 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.52 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.49 (d, *J* = 2.5 Hz, 1H), 7.42 (td, *J* = 7.6, 1.1 Hz, 1H), 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 7.23 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.65 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.30 (ddd, *J* = 7.9, 1.8, 0.9 Hz, 1H), 6.26 (dd, *J* = 2.5, 1.8 Hz, 1H), 3.89 (s, 3H), 3.49 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ 182.92, 162.16, 159.21, 155.65, 142.60, 141.63, 136.96, 133.36, 131.86, 129.72, 128.38, 127.96, 126.85, 126.15, 126.06, 122.64, 121.87, 120.69, 120.45, 119.83, 117.62, 114.07, 112.62, 112.26, 111.19, 110.92, 107.27, 64.86, 55.58, 54.74.
HRMS Calculated for $[C_{30}H_{22}N_2O_2+]$: 442.1681, found: 442.1672

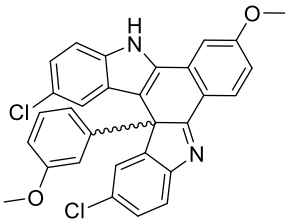
14b-(3,4-dimethoxyphenyl)-7,8-dimethoxy-5,14b-dihydrobenzo[a]indolo[2,3-c]carbazole (34)



Compound **34** was prepared analogously to GP2 procedure using **S10** (32.5 mg, 0.13 mmol) as substrate, oAC_{HNO3} (58 mg) and *R*-camphorsulfonic acid (58 mg, 0.26 mmol) instead of $MeSO_3H$. Reaction time was 17 h and temperature was 70 °C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex
(1:4->1:2->1:1) as eluent. Yield of **34** was 6.5 mg, 20%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.12 – 8.03 (m, 2H), 7.68 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.55 (s, 1H), 7.52 – 7.48 (m, 2H), 7.41 (td, *J* = 7.6, 1.1 Hz, 1H), 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 7.18 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.35 – 6.30 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.57 (s, 3H), 3.36 (s, 3H).
^{13}C NMR (126 MHz, DMSO) δ 183.76, 155.43, 151.74, 148.67, 148.43, 147.80, 142.13, 136.62, 133.70, 133.39, 128.21, 126.98, 126.05, 125.94, 124.04, 122.07, 121.94, 120.61, 120.23, 119.36, 117.75, 111.98, 111.85, 110.24, 109.70, 108.93, 105.78, 64.78, 55.86, 55.78, 55.35, 55.22.
HRMS Calculated for [$C_{32}H_{26}N_2O_4$+]: 502.1893, found: 502.1879

2,13-dichloro-7-methoxy-14b-(3-methoxyphenyl)-5,14b-dihydrobenzo[a]indolo[2,3-c]carbazole (35)

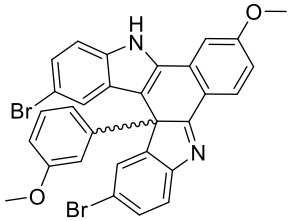


Compound **35** was prepared analogously to GP2 procedure using **S11** (31.3 mg, 0.12 mmol) as substrate, oAC_{HNO3} (56 mg) and *R*-camphorsulfonic acid (60 mg, 0.26 mmol) instead of $MeSO_3H$. Reaction time was 28 h and temperature was 90 °C. Product was filtered through celite with DCM. Yield of **35** was 11 mg, 35%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.32 (s, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.25 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.70 (ddd, *J* = 8.3, 2.5, 0.8 Hz, 1H), 6.30 (ddd, *J* = 7.9, 1.9, 0.9 Hz, 1H), 6.20 (dd, *J* = 2.5, 1.9 Hz, 1H), 3.89 (s, 3H), 3.52 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 183.35, 162.37, 159.33, 154.53, 143.36, 141.37, 135.39, 135.17, 131.27, 130.47, 130.11, 128.79, 128.18, 127.54, 125.69, 125.10, 122.72, 122.20, 121.58, 118.31, 117.66, 114.74, 113.98, 112.45, 111.35, 109.86, 107.66, 65.08, 55.65, 54.80.
HRMS Calculated for [$C_{30}H_{20}Cl_2N_2O_2$+]: 510.0902, found: 510.0898

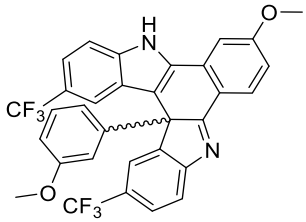
2,13-dibromo-7-methoxy-14b-(3-methoxyphenyl)-5,14b-dihydrobenzo[a]indolo[2,3-c]carbazole (36)



Compound **36** was prepared analogously to GP2 procedure using **S12** (39.3 mg, 0.13 mmol) as substrate, oAC$_{HNO3}$ (60 mg) and *R*-camphorsulfonic acid (60 mg, 0.26 mmol) instead of $MeSO_3H$. Reaction time was 30 h and temperature was 90 °C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4->1:2->1:1) as eluent. Yield of **36** was 15.1 mg, 39%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.07 – 8.02 (m, 2H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 2.5 Hz, 1H), 7.37 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.07 (t, *J* = 8.1 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.71 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.30 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.19 (t, *J* = 2.2 Hz, 1H), 3.88 (s, 3H), 3.53 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ 183.30, 162.39, 159.34, 154.91, 143.65, 141.29, 135.60, 135.01, 131.66, 131.23, 130.16, 128.39, 128.24, 125.23, 122.72, 121.57, 121.24, 118.66, 117.65, 114.77, 114.45, 113.05, 112.44, 111.35, 109.68, 107.72, 65.08, 55.66, 54.81, 39.52.
HRMS Calculated for [$C_{30}H_{20}{}^{79}Br^{81}BrN_2O_2$+]: 599.9871, found: 599.9848

7-methoxy-14b-(3-methoxyphenyl)-2,13-bis(trifluoromethyl)-5,14b-dihydrobenzo[a]indolo[2,3-c]carbazole (37)



Compound **37** was prepared analogously to GP2 procedure using **S13** (37.3 mg, 0.13 mmol) as substrate, oAC$_{HNO3}$ (60 mg) and *R*-camphorsulfonic acid (60 mg, 0.26 mmol) instead of $MeSO_3H$. Reaction time was 30 h and temperature was 90 °C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4->1:2->1:1->2:1) as eluent. Yield of **37** was 4.8 mg, 15%.

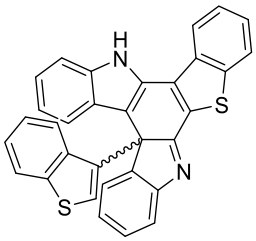
^{1}H NMR (500 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.28 – 8.23 (m, 1H), 8.21 – 8.16 (m, 1H), 7.96 – 7.91 (m, 2H), 7.89 – 7.85 (m, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 2.5 Hz, 1H), 7.54 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.08 (t, *J* = 8.1 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.72 (ddd, *J* = 8.3, 2.6,

0.8 Hz, 1H), 6.31 (ddd, *J* = 7.9, 1.9, 0.8 Hz, 1H), 6.19 (t, *J* = 2.2 Hz, 1H), 3.91 (s, 3H), 3.51 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 186.04, 162.75, 159.39, 159.05, 142.07, 140.72, 138.40, 135.90, 131.31, 130.33, 128.54, 126.57, 126.53, 126.17, 125.67, 125.14 (d, *J* = 271.1 Hz), 124.30 (d, *J* = 271.9 Hz), 122.04 – 121.19 (m, 3C), 119.06, 117.63, 116.12, 115.05, 113.54, 112.39, 111.59, 110.88, 108.02, 64.88, 55.73, 54.80.

HRMS Calculated for [$C_{32}H_{20}F_6N_2O_2$+]: 578.1429, found: 578.1415

15c-(benzo[b]thiophen-3-yl)-11,15c-dihydrobenzo[4,5]thieno[2,3-a]indolo[2,3-c]carbazole (38)



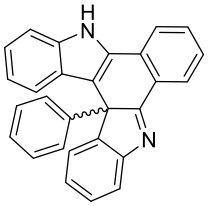
Compound **38** was prepared analogously to GP2 procedure using **S14** (32.5 mg, 0.13 mmol) as substrate, oAC$_{HNO3}$ (58 mg) and *R*-camphorsulfonic acid (59 mg, 0.25 mmol) instead of MeSO$_3$H. Reaction time was 22 h and temperature was 70°C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:2) as eluent. Yield of **38** was 5.0 mg, 14%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.63 (dt, *J* = 8.3, 0.9 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 7.4 Hz, 1H), 7.91 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.83 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.67 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.63 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.54 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 2H), 7.37 (td, *J* = 7.5, 1.1 Hz, 1H), 7.26 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.18 (dddd, *J* = 11.2, 8.0, 7.0, 1.1 Hz, 2H), 7.08 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 6.93 (s, 1H), 6.76 (dt, *J* = 8.4, 1.0 Hz, 1H).

^{13}C NMR (126 MHz, DMSO) δ 180.22, 156.43, 140.59, 140.45, 138.60, 136.66, 135.46, 133.71, 133.51, 131.01, 130.75, 129.87, 129.29, 127.35, 127.25, 126.74, 126.69, 126.25, 125.74, 124.31, 124.11, 123.95, 123.90, 123.36, 122.46, 121.47, 120.88, 120.79, 119.00, 114.14, 113.06, 64.72.

HRMS Calculated for [$C_{32}H_{18}N_2S_2$+]: 494.0911, found: 494.0913

14b-phenyl-5,14b-dihydrobenzo[a]indolo[2,3-c]carbazole (39)

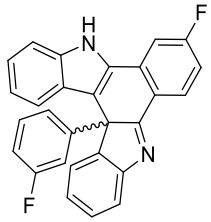


Compound **39** was prepared analogously to GP2 procedure using 2-phenyl-indole (0.47 g, 2.5 mmol) as substrate, oAC$_{HNO3}$ (1.7 g) and MeSO$_3$H (0.48 mL, 7.3 mmol). Reaction time was 17 h and temperature was 70°C. Product was purified using flash

column chromatography with silica as stationary phase and EtOAc:nHex (1:4 -> 1:1) as eluent. Yield of **39** was 5.7 mg, 1.2%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 7.4 Hz, 1H), 7.90 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.45 (td, *J* = 7.6, 1.1 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.22 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.13 – 7.01 (m, 3H), 6.78 – 6.70 (m, 2H).
^{13}C NMR (101 MHz, DMSO) δ 183.38, 155.43, 142.04, 140.48, 137.10, 133.38, 131.65, 130.30, 129.34, 128.76 (2C), 128.42, 128.11, 127.00, 126.90, 126.65, 126.29, 126.20, 125.46 (2C), 122.54, 122.03, 121.06, 120.44, 119.77, 112.30, 110.28, 65.08.
HRMS Calculated for [$C_{28}H_{18}N_2$+]: 382.1470, found: 382.1470

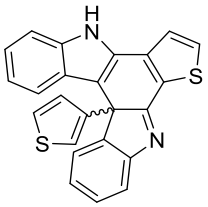
7-fluoro-14b-(3-fluorophenyl)-5,14b-dihydrobenzo[a]indolo[2,3-c]carbazole (40)



Compound **40** was prepared analogously to GP2 procedure using **S15** (0.53 g, 2.5 mmol) as substrate, oAC_{HNO3} (114 g) and $MeSO_3H$ (33 µL, 0.50 mmol). Reaction time was 26 h and temperature was 70 °C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **40** was 2.9 mg, 2.8%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.14 (s, 1H), 8.18 – 8.05 (m, 2H), 8.01 – 7.94 (m, 1H), 7.76 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.73 (dd, *J* = 9.9, 2.5 Hz, 1H), 7.55 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.48 (td, *J* = 7.6, 1.2 Hz, 1H), 7.39 (td, *J* = 7.5, 1.2 Hz, 1H), 7.31 – 7.20 (m, 2H), 7.22 – 7.12 (m, 2H), 6.94 (tdd, *J* = 8.5, 2.6, 0.9 Hz, 1H), 6.55 (ddd, *J* = 8.0, 1.8, 0.9 Hz, 1H), 6.43 (ddd, *J* = 10.5, 2.6, 1.8 Hz, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 181.56, 164.48 (d, *J* = 226.9 Hz), 162.03 (d, *J* = 223.7 Hz), 155.26, 143.15 (d, *J* = 6.3 Hz), 141.11, 137.17, 132.57 (d, *J* = 8.6 Hz), 132.52, 130.88 (d, *J* = 8.4 Hz), 129.01 (d, *J* = 9.2 Hz), 128.81, 126.95, 126.48, 126.21, 125.43 (d, *J* = 2.8 Hz), 123.22, 121.50 (d, *J* = 2.3 Hz), 121.23, 120.82, 119.94, 115.09 (d, *J* = 22.0 Hz), 114.16 (d, *J* = 20.9 Hz), 112.51, 112.35 (d, *J* = 22.5 Hz), 110.87, 109.26 (d, *J* = 24.7 Hz), 64.62.
HRMS Calculated for [$C_{28}H_{16}F_2N_2$+]: 418.1282, found: 418.1264

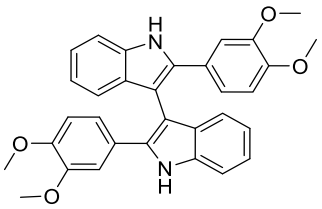
13c-(thiophen-3-yl)-9,13c-dihydroindolo[2,3-c]thieno[2,3-a]carbazole (41)



Compound **41** was prepared analogously to GP2 procedure using **S16** (0.50 g, 2.5 mmol) as substrate, oAC_{HNO3} (114 g) and $MeSO_3H$ (33 µL, 0.50 mmol). Reaction time was 20 h and temperature was 70°C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **123** was 18.9 mg, 38%.

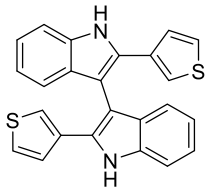
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.22 (d, *J* = 7.4 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 5.1 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.63 (d, *J* = 5.1 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H), 7.36 (td, *J* = 7.5, 1.2 Hz, 1H), 7.26 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.16 (td, *J* = 7.5, 7.1, 1.3 Hz, 1H), 6.60 (dd, *J* = 3.0, 1.4 Hz, 1H), 6.51 (dd, *J* = 5.1, 1.4 Hz, 1H).
^{13}C NMR (101 MHz, DMSO) δ 179.24, 155.41, 141.64, 140.72, 137.39, 136.38, 132.54, 130.78, 129.12, 128.61, 126.84, 126.20, 125.94, 125.77, 125.61, 123.19, 122.27, 121.03, 120.43, 120.29, 119.72, 113.33, 112.34, 64.62.
HRMS Calculated for [$C_{28}H_{16}F_2N_2$+]: 394.0598, found: 394.0602

2,2'-bis(3,4-dimethoxyphenyl)-1H,3'H-3,3'-biindole (42)



Compound **42** was prepared following the GP1 with **S10** (31.7 mg, 0.13 mmol) and oAC_{HNO3} (56.7 mg) with 21 h reaction time at 80°C. Product was filtered through celite with DCM and purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4->1:2->1:1) as eluent. Yield of **42** was 19.4 mg, 61%.
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.49 (s, 2H), 7.46 (dt, *J* = 8.2, 0.9 Hz, 2H), 7.16 (dd, *J* = 8.4, 2.1 Hz, 2H), 7.13 – 7.06 (m, 4H), 6.99 – 6.93 (m, 2H), 6.86 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.66 (s, 6H), 3.25 (s, 6H).
^{13}C NMR (126 MHz, DMSO) δ 148.16, 147.80, 136.23, 134.71, 129.94, 125.46, 121.46, 119.01 (2C), 118.52, 111.69, 110.97, 110.09, 105.50, 55.35, 54.57.
HRMS Calculated for [$C_{32}H_{28}N_2O_4$+]: 504.2049, found: 504.2027

2,2'-di(thiophen-3-yl)-1H,3'H-3,3'-biindole (43)



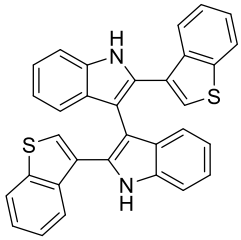
Compound **43** was prepared following the GP1 with **S16** (0.51 mg, 0.25 mmol) and oAC_{HNO3} (56.6 mg) with 24 h reaction time at 70°C. Product was filtered through celite with DCM and purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9->1:4->1:1) as eluent. Yield of **43** was 28.6 mg, 57%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 2H), 7.52 (dd, *J* = 3.0, 1.3 Hz, 2H), 7.47 (dt, *J* = 8.1, 0.9 Hz, 2H), 7.36 (dd, *J* = 5.1, 3.0 Hz, 2H), 7.12 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 2H), 7.07 (dd, *J* = 5.1, 1.3 Hz, 2H), 6.94 (dt, *J* = 7.9, 0.8 Hz, 2H), 6.86 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO) δ 136.13, 133.84, 131.42, 129.49, 126.23, 125.89, 121.80, 120.55, 119.14 (2C), 111.12, 105.44.

HRMS Calculated for [$C_{32}H_{28}N_2O_4$+]: 396.0755, found: 396.0755

2,2'-bis(benzo[b]thiophen-3-yl)-1H,3'H-3,3'-biindole (44)



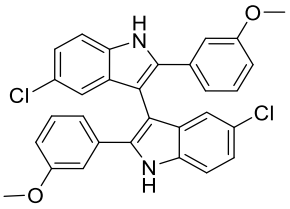
Compound **44** was prepared following the GP1 with **S14** (0.35 mg, 0.14 mmol) and oAC_{HNO3} (33.4 mg) with 24 h reaction time at 70°C. Product was filtered through celite with DCM and purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9->1:6) as eluent. Yield of **44** was 16.5 mg, 47%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.38 (m, 4H), 7.21 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 2H), 7.16 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 2H), 7.06 – 6.99 (m, 4H), 6.95 (s, 2H), 6.89 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 2H).

^{13}C NMR (126 MHz, DMSO) δ 139.16, 136.93, 136.32, 130.20, 129.02, 128.52, 125.20, 123.91, 123.48, 122.52, 122.28, 121.43, 119.56, 119.06, 111.34, 107.38.

HRMS Calculated for [$C_{32}H_{20}N_2S_2$+]: 496.1068, found: 496.1050

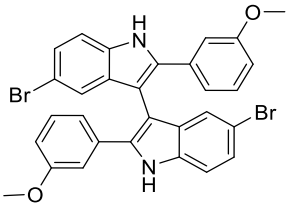
5,5'-dichloro-2,2'-bis(3-methoxyphenyl)-1H,3'H-3,3'-biindole (45)



Compound **45** was prepared analogously to GP2 procedure using **S11** (32.9 mg, 0.13 mmol) as substrate, oAC_{HNO3} (60 mg) and R-camphorsulfonic acid (57 mg, 0.25 mmol) instead of $MeSO_3H$. Reaction time was 22 h and temperature was 70°C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9->1:4) as eluent. Yield of **45** was 18.1 mg, 55%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.20 – 7.10 (m, 6H), 7.07 (dd, *J* = 2.6, 1.5 Hz, 2H), 6.87 (d, *J* = 2.0 Hz, 2H), 6.76 (ddd, *J* = 8.0, 2.6, 1.2 Hz, 2H), 3.49 (s, 6H).
^{13}C NMR (126 MHz, DMSO) δ 159.09, 136.41, 134.77, 133.27, 130.51, 129.66, 123.92, 122.01, 118.66, 117.83, 113.30, 113.04, 111.74, 105.32, 54.64.
HRMS Calculated for [$C_{30}H_{22}N_2O_2$+]: 504.2049, found: 504.2027

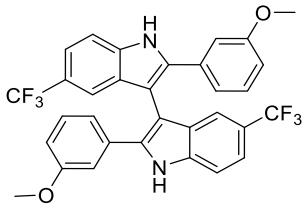
5,5'-dibromo-2,2'-bis(3-methoxyphenyl)-1H,1'H-3,3'-biindole (46)



Compound **46** was prepared following the GP1 with **S12** (0.37 mg, 0.12 mmol) and oAC_{HNO3} (59.9 mg) with 22 h reaction time at 70°C. Product was filtered through celite with DCM and purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **46** was 37.2 mg, 51%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.90 (s, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.24 (dd, *J* = 8.6, 2.0 Hz, 2H), 7.17 (t, *J* = 7.9 Hz, 2H), 7.12 (dt, *J* = 7.9, 1.3 Hz, 2H), 7.06 (dd, *J* = 2.6, 1.6 Hz, 2H), 7.00 (d, *J* = 1.9 Hz, 2H), 6.76 (ddd, *J* = 8.1, 2.6, 1.1 Hz, 2H), 3.49 (s, 6H).
^{13}C NMR (101 MHz, DMSO) δ 159.11, 136.25, 134.99, 133.20, 131.20, 129.70, 124.56, 120.85, 118.66, 113.53, 113.36, 111.87, 111.74, 105.15, 54.66.
HRMS Calculated for [$C_{30}H_{22}{}^{79}Br^{81}BrN_2O_2$+]: 602.0028, found: 602.0002

2,2'-bis(3-methoxyphenyl)-5,5'-bis(trifluoromethyl)-1H,3'H-3,3'-biindole (47)



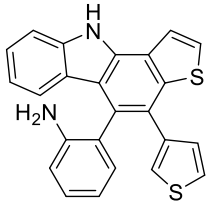
Compound **47** was prepared following the GP1 with **S13** (0.37 mg, 0.14 mmol) and oAC_{HNO3} (57.6 mg) with 22 h reaction time at 70°C. Product was filtered through celite with DCM and purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4->1:2->1:1) as eluent. Yield of **47** was 22.6 mg, 61%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 12.18 (s, 2H), 7.68 (dt, *J* = 8.5, 0.7 Hz, 2H), 7.43 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.23 – 7.15 (m, 4H), 7.14 (dt, *J* = 7.8, 1.3 Hz, 2H), 7.08 (dd, *J* = 2.6, 1.5 Hz, 2H), 6.78 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 2H), 3.48 (s, 6H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 159.16, 137.91, 137.15, 133.05, 129.74, 128.35, 125.29 (q, *J* = 270.5 Hz), 120.22 (q, *J* = 31.0 Hz), 119.01, 118.40 (q, *J* = 3.9 Hz), 116.26 (q, *J* = 4.6 Hz), 113.65, 112.30, 112.01, 106.14, 54.68.

HRMS Calculated for $[C_{32}H_{22}F_6N_2O_2+]$: 580.1585, found: 580.1577

2-(4-(thiophen-3-yl)-10H-thieno[3,2-a]carbazol-5-yl)aniline (48)



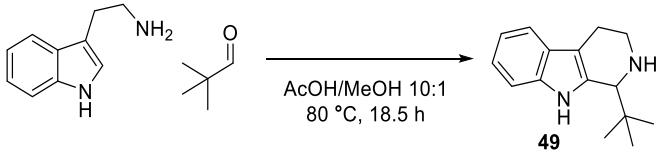
Compound **48** was prepared analogously to GP2 procedure but without any oAC, using **43** (7.1 mg, 18 μmol) as substrate and $MeSO_3H$ (2 μL, 35 μmol). Reaction time was 16 h and temperature was 70°C. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4->1:2) as eluent. Yield of **48** was 7.0 mg, 99%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.97 (d, *J* = 5.5 Hz, 1H), 7.80 (d, *J* = 5.5 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.43 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.17 – 7.07 (m, 2H), 6.91 – 6.82 (m, 2H), 6.76 (ddd, *J* = 7.6, 6.3, 1.1 Hz, 2H), 6.58 (td, *J* = 7.3, 1.2 Hz, 1H), 4.43 (s, 2H).

^{13}C NMR (101 MHz, DMSO) δ 146.13, 139.77, 139.55, 138.97, 133.96, 130.23, 129.17, 128.99, 128.37, 126.40, 124.91, 124.34, 124.09, 123.87, 123.58, 123.22, 121.78, 121.06, 120.95, 118.70, 117.39, 116.31, 114.31, 110.90.

HRMS Calculated for $[C_{24}H_{16}N_2S_2+]$: 396.0755, found: 396.0771

1-*tert*-Butyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (49)



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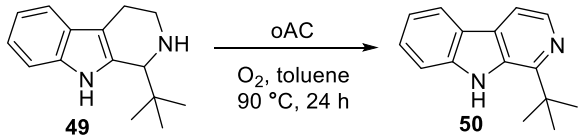
The reaction was performed according to a modified method of YE *et al*.[164] Pivaldehyde (1.96 mL, 18.0 mmol, 1.94 eq) was added to a solution of tryptamine (1.50 g, 9.36 mmol, 1.00 eq) in AcOH/MeOH (10:1, 7.50 mL). The reaction was stirred at 80 °C for 18.5 h. After cooling to r.t., the solution was basified to pH = 10 with $NH_3 \cdot H_2O$ (aq. 25%). Dist. H_2O (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (1 x 40 mL, 3 x 30 mL). The combined organic phases were washed with brine (30 mL), which was then extracted with CH_2Cl_2 (2 x 20 mL). The organic phases were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash chromatography (CH_2Cl_2/MeOH 5% → 15%), which gave an orange oil. Upon adding hexane (20 mL) a pale-yellow solid precipitated, which was filtered off and washed with ice-cold hexane (30 mL). The filtrate-solvent was removed under reduced pressure, giving a pale-yellow solid. Both were combined to give **49** (1.53 g, 6.70 mmol, 72%). Spectroscopic data matches with recorded literature values[165].

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.12 (s, 1H, N*H*), 7.35 (d, ^3J = 8.2 Hz, 2H, 2 x C*H*), 7.00 (ddd, ^3J = 8.1 Hz, ^3J = 6.9 Hz, ^4J = 1.3 Hz, 1H, C*H*), 6.92 (ddd, ^3J = 7.9 Hz, ^3J = 6.8 Hz, ^4J = 1.0 Hz, 1H, C*H*), 3.71 (s, 1H, C*H*), 3.18 (dt, ^2J = 11.8 Hz, ^3J = 4.3 Hz, 1H, C*H*H), 2.73 (dt, ^2J = 12.6 Hz, ^3J = 6.3 Hz, 1H, C*H*H), 2.57-2.58 (m, 2H, CH_2), 1.01 (s, 9H, 3 x CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 136.0, 135.0, 127, 120.3, 118.0, 117.1, 111.2, 110.0, 61.3, 42.7, 35.6, 3 x 27.4, 22.7.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{15}H_{21}N_2$ $(M+H)^+$: 229.1699, found: 229.1692.
TLC R_f = 0.32 (CH_2Cl_2/MeOH 10%).

1-(*tert*-Butyl)-1*H*-pyrido[3,4-*b*]indole (50)



49 **50**

GENERAL PROCEDURE

1-*tert*-Butyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**49**, 57.1 mg, 250 µmol, 1.00 eq), oAC and toluene (1.00 mL) were placed in a reaction tube under an oxygen atmosphere. It was stirred for 24 hours at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 400 mL). The solvent was removed under reduced pressure to give the crude product (**50**) as a dark-yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.14 (s, 1H, N*H*), 8.24 (d, ^3J = 5.2 Hz, 1H, C*H*), 8.18 (d, ^3J = 7.9 Hz, 1H, C*H*), 7.97 (dd, ^3J = 5.2 Hz, ^5J = 0.5 Hz, 1H, C*H*), 7.67 (d, ^3J = 8.2 Hz, 1H, C*H*), 7.52

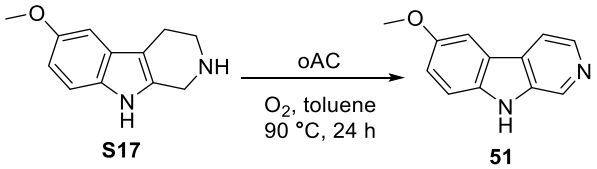
(ddd, ^3J = 8.2 Hz, ^3J = 7.1 Hz, ^4J = 1.2 Hz, 1H, C*H*), 7.21 (ddd, ^3J = 7.9 Hz, ^3J = 7.0 Hz, ^4J = 0.9 Hz, 1H, C*H*), 1.55 (s, 3 x CH_3).

^{13}C-NMR (101 MHz, DMSO-d_6) δ = 151.8, 140.2, 136.5, 132.0, 128.3, 127.7, 121.1, 120.5, 119.1, 113.0, 112.1, 37.5, 3 x 28.9.

HRMS (**ESI$^+$**) *m/z* calculated for $C_{15}H_{17}N_2$ $(M+H)^+$: 225.1386, found: 225.1380.

TLC R_f = 0.36 (CH_2Cl_2/MeOH 10%).

6-Methoxy-1*H*-pyrido[3,4-*b*]indole (51)



S17 **51**

The general procedure used for **50** was followed. 1,2,3,4-Tetrahydro-6-methoxy-1*H*-pyrido[3,4-*b*]indole (**S17**, 50.6 mg, 250 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 224 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 3 % → 8 %), which gave **51** (8 mg, 40.4 µmol, 16%) as a yellow solid. In a second reaction with oAC_{air} (n = 4.00, 224 mg) in toluene (1.50 mL), an NMR-yield of 38 % was obtained. ^{1}H-NMR data matches with recorded literature values[166].

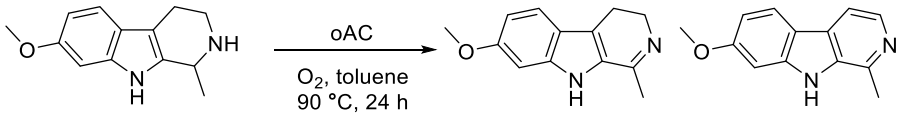
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.41 (s, 1H, N*H*), 8.86 (s, 1H, C*H*), 8.29 (d, ^3J = 5.2 Hz, 1H, C*H*), 8.09 (d, ^3J = 5.2 Hz, 1H, C*H*), 7.78 (d, ^4J = 2.9 Hz, 1H, C*H*), 7.51 (d, ^3J = 8.8 Hz, 1H, C*H*), 7.19 (dd, ^3J = 8.8 Hz, ^4J = 2.6 Hz, 1H, C*H*), 3.86 (s, 3H, CH_3).

^{13}C-NMR (101 MHz, DMSO-d_6) δ = 153.3, 137.3, 136.5, 135.4, 134.0, 127.4, 120.9, 118.2, 114.7, 112.8, 103.6, 55.6.

HRMS (**ESI$^+$**) *m/z* calculated for $C_{12}H_{11}N_2O$ $(M+H)^+$: 199.0866, found: 199.0861.

TLC R_f = 0.39 (CH_2Cl_2/MeOH 10%).

Harmine (52)



S18 **S19** **52**

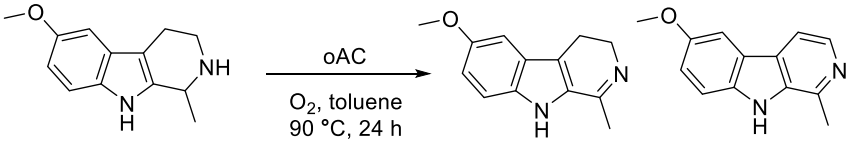
The general procedure was followed. **S18** (53.8 mg, 249 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 224 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 8% → 15%), which gave the fully oxidized **52** (5 mg, 23.6 µmol, 9%) as well as the intermediate **S19** (8 mg, 37.3 µmol, 15%), both as colorless solids. In a second reaction with oAC_{air} (n = 4.00, 224 mg) in toluene

(1.50 mL), NMR-yields of 12 % for **52** as well as 3 % for **S19** were obtained. Spectroscopic data of **52** matches with recorded literature values.[167]

52 (*fully oxidized*)
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.6 (s, 1H, N*H*), 8.17 (d, ^3J = 5.4 Hz, 1H, C*H*), 8.08 (d, ^3J = 8.7 Hz, 1H, C*H*), 7.87 (d, ^3J = 5.4 Hz, 1H, C*H*), 7.02 (d, ^4J = 2.2 Hz, 1H, C*H*), 6.86 (dd, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 1H, C*H*), 3.88 (s, 3 H, OCH_3), 2.74 (s, 3 H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 160.3, 142.3, 140.8, 136.8, 134.4, 127.7, 122.8, 114.7, 112.1, 109.4, 94.5, 55.3, 19.8.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{13}H_{13}N$ $(M+H)^+$: 213.1022, found: 213.1026.
TLC R_f = 0.47 (CH_2Cl_2/MeOH 15%).

S19 (*intermediate*)
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 12.48 (s, 1H, N*H*), 7.66 (d, ^3J = 9.0 Hz, 1H, C*H*), 6.91 (d, ^4J = 2.1 Hz, 1H, C*H*), 6.84 (dd, ^3J = 8.9 Hz, ^4J = 2.2 Hz, 1H, C*H*), 3.85 (s, 3H, OCH_3), 3.83 (t, ^3J = 8.6 Hz, 2H, CH_2), 3.14 (t, ^3J = 8.8 Hz, 2H, CH_2), 2.69 (s, 3 H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6): δ = 165.0, 160.6, 142.4, 125.6, 124.3, 123.0, 118.7, 113.9, 93.7, 55.4, 41.5, 18.9, 18.5.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{13}H_{15}N_2$ $(M+H)^+$: 215.1179, found: 215.1171.
TLC R_f = 0.41 (CH_2Cl_2/MeOH 15%).

Isoharmine (53)

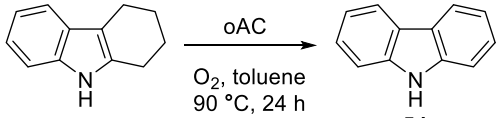


S20 **S21** **53**

The general procedure was followed. 1,2,3,4-Tetrahydroisoharmine (**S20**, 54.0 mg, 250 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 224 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 3% → 17%), which gave **53** (6.1 mg, 28.7 µmol, 11%) as well as the intermediate **S21** (6.9 mg, 32.2 µmol, 13 %), both as orange solids. **S21** could not be purified. In a second reaction with oAC_{air} (n = 4.00, 224 mg), an NMR-yield of 7 % was obtained. Spectroscopic data matches with recorded literature values.[168]

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.42 (s, 1H, N*H*), 8.26 (d, ^3J = 5.4 Hz, 1H, C*H*), 7.93 (d, ^3J = 5.4 Hz, 1H, C*H*), 7.74 (d, ^4J = 2.5 Hz, 1H, C*H*), 7.51 (d, ^3J = 8.8 Hz, 1H, C*H*), 7.18 (dd, ^3J = 8.8 Hz, ^4J = 2.6 Hz, 1H, C*H*), 3.85 (s, 3H, CH_3), 2.75 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 153.3, 142.0, 136.4, 135.4, 135.0, 126.9, 121.3, 118.1, 2 x 112.8, 103.5, 55.6, 20.1.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{13}H_{13}N_2O$ $(M+H)^+$: 213.1022, found: 213.1018.
TLC R_f = 0.26 (CH_2Cl_2/MeOH 10%).

Carbazole (54)

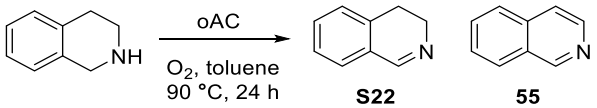


54

The general procedure was followed. 1,2,3,4-Tetrahydrocarbazole (43.3 mg, 253 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.00, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 200 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (hexane/EtOAc 9:1 → 6:1 → 4:1), which gave **54** (32.9 mg, 197 µmol, 78%) as a colorless solid. Spectroscopic data matches with recorded literature values[169].

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.23 (s, 1H, N*H*), 8.09 (d, ^3J = 7.9 Hz, 2H, 2 x C*H*), 7.48 (dt, ^3J = 8.1 Hz, ^3J = 0.8 Hz, 2H, 2 x C*H*), 7.38 (ddd, ^3J = 8.2 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 2H, 2 x C*H*), 7.15 (ddd, ^3J = 7.9 Hz, ^3J = 7.0 Hz, ^4J = 0.9 Hz, 2H, 2 x C*H*).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 139.7, 125.5, 122.3, 120.1, 118.4, 110.8.
TLC R_f = 0.46 (hexane/EtOAc 4:1).

Isoquinoline (55)



S22 **55**

The general procedure was followed. 1,2,3,4-Tetrahydroisoquinoline (31.7 µL, 250 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 224 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 0% → 5%), which gave the fully oxidized **55** (12 mg, 93.5 µmol, 37%) as well as the intermediate **S22** (12 mg, 91.0 µmol, 36%), both as a yellow oil. In a second reaction with oAC_{air} (n = 4.00, 224 mg) in toluene (1.00 mL), NMR-yields of 40% for **55** as well as 4% **S22** were obtained. An additional control test was run in the same conditions for 30 minutes giving 50% **S22** and 2% **55**. A reaction with oAC_{air} (n = 4.00, 224 mg) at 100 °C in toluene (1.50 mL) over 3 d gave an NMR-yield of 67% **55**. Spectroscopic data matches with recorded literature values.[170]

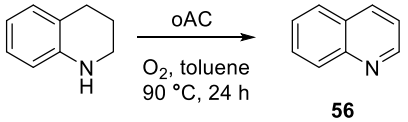
55 (*fully oxidized*)
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.27 (s, 1H, C*H*), 8.54 (d, ^3J = 5.4 Hz, 1H, C*H*), 7.98 (dd, ^3J = 8.2 Hz, ^4J = 0.9 Hz, 1H, C*H*), 7.82 (d, ^3J = 7.7 Hz, 1H, C*H*), 7.70 (ddd, ^3J = 8.2 Hz, ^3J = 6.9 Hz, ^4J = 1.3 Hz, 1H, C*H*), 7.66 (d, ^3J = 5.7 Hz, 1H, C*H*) 7.82 (d, ^3J = 7.7 Hz, 1H, C*H*), 7.61 (ddd, ^3J = 8.1 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 152.7 (*C*H), 143.2 (*C*H), 135.9 (*C*H), 130.5 (*C*H), 128.9 (*C*H), 127.8 (*C*H), 127.4 (*C*H), 126.6 (*C*H), 120.6 (*C*H).

HRMS (**ESI**$^+$) *m/z* calculated for C_9H_8N $(M+H)^+$: 130.0651, found: 130.0647.
TLC R_f = 0.59 (CH_2Cl_2/MeOH 10%).

S22 (*intermediate*)
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.35 (s, 1H, C*H*), 7.32-7.28 (m, ^3J = 7.7 Hz, 3H, 3 x C*H*), 7.16 (d, ^3J = 7.2 Hz, 1H, C*H*), 3.80-3.76 (d, ^3J = 7.7 Hz, 2H, CH_2), 2.76 (t, ^3J = 7.8 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.5 (*C*H), 136.5 (*C*), 132.3 (*C*), 131.2 (*C*H), 127.6 (*C*H), 127.3 (*C*H), 127.2 (*C*H), 47.5 (*C*H), 25.2 (*C*Ha).
HRMS (**ESI**$^+$) *m/z* calculated for $C_9H_{10}N$ $(M+H)^+$: 132.0808, found: 132.0817.
TLC R_f = 0.51 (CH_2Cl_2/MeOH 10%).

Due to their close R_f it was not possible to fully separate the product and the intermediate via flash chromatography, giving a 15% impurity of **139** in the spectrum of **S21**. This value was included into the total yield of both compounds.

Quinoline (56)

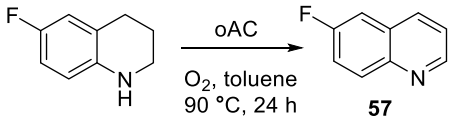


56

The general procedure was followed. 1,2,3,4-Tetrahydroquinoline (33.3 mg, 250 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 0% → 10%), which gave **56** (29 mg, 225 µmol, 90%) as a yellow oil. Spectroscopic data matches with recorded literature values.[171] Additional control tests were run: oAC_{air} (n = 4.00, 225 mg) in the same conditions gave **56** (33 mg, 255 µmol, >99%). oAC_{air} (n = 4.00, 225 mg) and a reaction time of 30 min gave an NMR-yield of 53 % **56**. The same conditions were used to run a test in presence of TEMPO (1 eq) for 3h, the yield was determined with NMR as 52% **56**. The same conditions were used as well to run a test for 30 minutes in trifluorotoluene. The yield was determined with NMR as 50% **56**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.93 (dd, ^3J = 4.1 Hz, ^4J = 1.6 Hz, 1H, C*H*), 8.17 (d, ^3J = 8.2 Hz, 1H, C*H*), 8.12 (d, ^3J = 8.5 Hz, 1H, C*H*), 7.82 (d, ^3J = 8.1 Hz, 1H, C*H*), 7.72 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.5 Hz, 1H, C*H*), 7.56 (ddd, ^3J = 8.1 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, C*H*), 7.40 (dd, ^3J = 8.3 Hz, ^3J = 4.1 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 150.4, 148.3, 136.1, 2 x 129.5, 128.3, 127.8, 126.6, 121.1.
HRMS (**ESI**$^+$) *m/z* calculated for C_9H_8N $(M+H)^+$: 130.0651, found: 130.0653.
TLC R_f = 0.56 (CH_2Cl_2/MeOH 10%).

6-Fluoroquinoline (57)

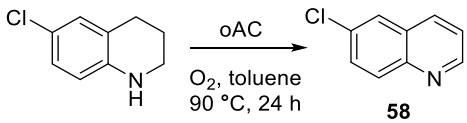


57

The general procedure was followed. 6-Fluoro-1,2,3,4-tetrahydroquinoline (37.8 mg, 250 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 0% → 10%), which gave **57** (18.2 mg, 124 µmol, 50 %) as a yellow oil. In a second reaction, an NMR-yield of 97 % was obtained. Spectroscopic data matches with recorded literature values.[172] An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 64 % **57**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.89 (dd, ^3J = 4.3 Hz, ^4J = 1.5 Hz, 1H, C*H*), 8.13-8.09 (m, 2H, 2 x C*H*), 7.52-7.47 (m, 1H, C*H*), 7.45-7.40 (m, 2H, 2 x C*H*).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.5 (d, ^3J = 248.1 Hz), 149.8 (d, ^3J = 3.3 Hz), 145.5, 135.6 (d, ^3J = 6.1 Hz), 132.2 (d, ^3J = 9.1 Hz), 129.0 (d, ^3J = 9.8 Hz), 121.9, 119.8 (d, ^3J = 26.5 Hz), 110.8 (d, ^3J = 22.2 Hz)
^{19}F-NMR (376 MHz, $CDCl_3$) δ = 113.8.
TLC R_f = 0.49 (CH_2Cl_2/MeOH 5 %).

6-Chloroquinoline (58)

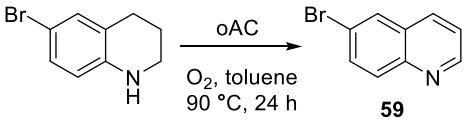


58

The general procedure was followed. 6-Chloro-1,2,3,4-tetrahydroquinoline (16.7 mg, 100 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.00, 89.6 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and a yield of 72 % determined through NMR. Spectroscopic data matches with recorded literature values.[172] An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 60 % **58**.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 8.93 (dd, ^3J = 4.2 Hz, ^3J = 1.7 Hz, 1H, C*H*), 8.36 (dd, ^3J = 8.3 Hz, ^4J = 1.1 Hz, 1H, C*H*), 8.13 (d, ^4J = 2.4 Hz, 1H, C*H*), 8.04 (d, ^3J = 9.0 Hz, 1H, C*H*), 7.77 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H, C*H*), 7.59 (dd, ^3J = 8.3 Hz, ^3J = 4.2 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 151.1, 146.1, 135.4, 131.1, 130.9, 130.0, 128.7, 126.8, 122.4.
TLC R_f = 0.60 (CH_2Cl_2/MeOH 10%).

6-Bromoquinoline (59)



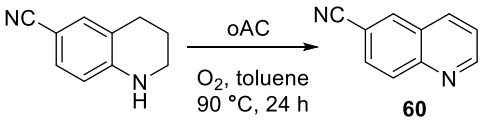
59

The general procedure was followed. 6-Bromo-1,2,3,4-Tetrahydroquinoline (53.7 mg, 253 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.00, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2) which gave impure **59** (39.5 mg, 190 µmol, 75 %) as a yellow oil, which could not be further purified. In a second reaction, an NMR-yield of 66 % was obtained. An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 55 % **59**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.93 (dd, ^3J = 4.2 Hz, ^4J = 1.6 Hz, 1H, C*H*), 8.08 (d, ^3J = 8.3 Hz, 1H, C*H*), 7.99 (s, 1H, C*H*), 7.98 (d, ^3J = 7.5 Hz, 1H, C*H*), 7.78 (dd, ^3J = 8.9 Hz, ^3J = 2.3 Hz), 7.43 (dd, ^3J = 8.2 Hz, ^3J = 4.2 Hz, 1H, C*H*).

TLC R_f = 0.49 (CH_2Cl_2/MeOH 5%).

Quinoline-6-carbonitrile (60)

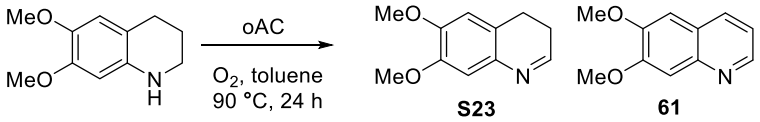


60

The general procedure was followed. 1,2,3,4-Tetrahydroquinoline-6-carbonitrile (15.8 mg, 100 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.00, 89.6 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and a yield of 72 % determined through NMR. Spectroscopic data matches with recorded literature values.[173] An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 27 % **60**.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 9.08 (dd, ^3J = 4.4 Hz, ^3J = 1.7 Hz, 1H, C*H*), 8.67 (d, ^4J = 1.9 Hz, 1H, C*H*), 8.50 (d, ^3J = 8.6 Hz, ^4J = 1.0 Hz, 1H, C*H*), 8.16 (d, ^3J = 8.7 Hz, 1H, C*H*), 8.04 (dd, ^3J = 8.7 Hz, ^4J = 1.9 Hz, 1H, C*H*), 7.70 (dd, ^3J = 8.3 Hz, ^3J = 4.3 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 153.7, 148.5, 136.8, 135.0, 130.6, 130.2, 127.3, 123.0, 118.6, 109.1.
TLC R_f = 0.60 (CH_2Cl_2/MeOH 10%).

6,7-Dimethoxyquinoline (61)

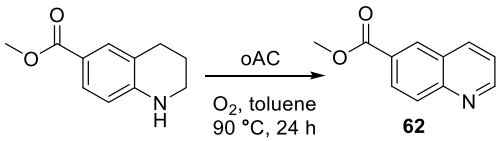


The general procedure was followed. 1,2,3,4-Tetrahydro-6,7-dimethoxyquinoline (57.1 mg, 295 µmol, 1.18 eq), $oAC_{air(\Delta)}$ (n = 4.00, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 200 mL/12 %, 100 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 2 % → 5 % → 10 %), which gave **61** (16.8 mg, 88.7 µmol, 30 %) as well as 3,4-dihydro-6,7-dihydroxyquinoline **S23** (25.7 mg, 134 µmol, 49 %) both as a yellow oil. Spectroscopic data for **61** matches with recorded literature values.[174] An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 61% **S23** and 3% **61**.

61 (*fully oxidized*)
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.05 (s, 1H, C*H*), 8.31 (d, ^3J = 5.7 Hz, 1H, C*H*), 7.64 (d, ^3J = 5.5 Hz, 1H, C*H*), 7.47 (s, 1H, C*H*), 7.33 (s, 1H, C*H*), 3.92 (s, 3H, CH_3), 3.92 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 152.7, 150.0, 149.7, 141.5, 131.9, 124.4, 119.1, 105.5, 104.8.
TLC R_f = 0.42 (CH_2Cl_2/MeOH 10 %).

S23 (*intermediate*)
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.21 (t, ^3J = 2.0 Hz, 1H, C*H*), 7.03 (s, 1H, C*H*), 6.85 (s, 1H, C*H*), 3.79 (s, 3H, CH_3), 3.76 (s, 3H, CH_3). 3.60-3.55 (m, 2H, CH_2), 2.60 (t, ^3J = 7.9 Hz, 2H, CH_2).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 159.0, 150.9, 147.5, 129.3, 121.0, 110.9, 110.8, 55.7. 55.6, 46.7, 24.0.
TLC R_f = 0.28 (CH_2Cl_2/MeOH 10 %).

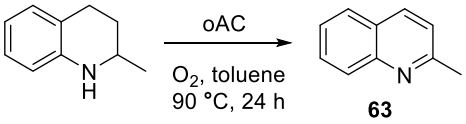
Methyl quinoline-6-carboxylate (62)



The general procedure was followed. Methyl 1,2,3,4-tetrahydro-6-quinolinecarboxylate (40.5 mg, 212 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.7, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2), which gave **62** (32.6 mg, 174 µmol, 82 %) as a beige solid. In a second reaction, an NMR-yield of 96 % was obtained. Spectroscopic data matches with recorded literature values.[175] An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 34 % **62**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.01 (dd, ^3J = 4.3 Hz, ^4J = 1.7 Hz, 1H, C*H*), 8.59 (d, ^4J = 1.9 Hz, 1H, C*H*), 8.29 (dd, ^3J = 8.8 Hz, ^4J = 2.0 Hz, 1H, C*H*), 8.26 (dd, ^3J = 8.3 Hz, ^3J = 1.2 Hz, 1H, C*H*), 8.14 (d, ^3J = 8.8 Hz, 1H, C*H*), 7.48 (dd, ^3J = 8.3 Hz, ^3J = 4.1 Hz, 1H, C*H*), 3.99 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 166.7, 152.7, 150.2, 137.5, 131.1, 130.0, 129.1, 128.3, 127.6, 122.0, 52.6.
TLC R_f = 0.49 (CH_2Cl_2/MeOH 5%).

Quinaldine (63)

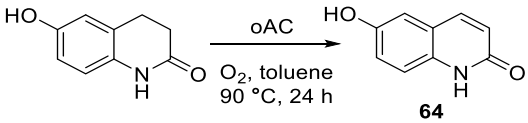


63

The general procedure was followed. 1,2,3,4-Tetrahydroquinaldine (36.1 µL, 250 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.00, 224 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of Celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 0% → 5%), which gave **63** (19 mg, 133 µmol, 53%) as a colorless oil. An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 36 % **63**. In a reaction with oAC_{HNO3} (n = 4.00, 224 mg) in toluene (1.00 mL), a yield of 56 % (20 mg, 140 µmol) was obtained. Spectroscopic data matches with recorded literature values.[175]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.24 (d, ^3J = 8.5 Hz, 1H, C*H*), 7.91 (d, ^3J = 8.5 Hz, 2H, 2 x C*H*), 7.70 (ddd, ^3J = 8.4 Hz, ^3J = 6.9 Hz, ^4J = 1.4 Hz, 1H, C*H*), 7.53 (ddd, ^3J = 8.0 Hz, ^3J = 6.9 Hz, ^4J = 1.1 Hz, 1H, C*H*), 7.41 (d, ^3J = 8.5 Hz, 1H, C*H*), 2.65 (s, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 158.7, 147.3, 136.0, 129.3, 128.2, 127.7, 126.2, 125.6, 122.1, 24.8.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{10}H_{10}N$ $(M+H)^+$: 144.0808, found: 144.0806.
TLC R_f = 0.56 (CH_2Cl_2/MeOH 10%).

6-Hydroxyquinolin-2(1*H*)-one (64)



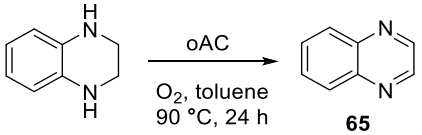
64

The general procedure was followed. 6-Hydroxy-3,4-dihydro-2-(1*H*)-quinolinone (40.8 mg, 250 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 224 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 3% → 15%), which gave **64** (22 mg, 137 µmol, 55%) as a colorless solid. In a second reaction with oAC_{air} (n = 4.00, 224 mg) in toluene (1.00 mL), a yield of 47 % (29 mg, 118 µmol) was

obtained. A reaction with oAC_{air} (n = 4.00, 224 mg) in anisole (1.50 mL) at 140 °C over 3 d gave an NMR-yield of 47 %. Spectroscopic data matches with recorded literature values.[176]

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.49 (s, 1H, O*H*), 10.09 (s, 1H, O*H*), 7.73 (d, ^3J = 9.0 Hz, 1H, C*H*), 7.44 (d, ^3J = 8.5 Hz, 1H, C*H*), 6.68 (d, ^4J = 2.3 Hz, 1H, C*H*), 6.62 (dd, ^3J = 8.5 Hz, ^4J = 2.3 Hz, 1H, C*H*), 6.21 (d, ^3J = 9.5 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 162.3, 159.3, 140.8, 140.1, 129.3, 117.5, 112.4, 111.5, 99.8.
HRMS (**ESI$^+$**) *m/z* calculated for $C_9H_8NO_2$ $(M+H)^+$: 162.0550, found: 162.0559.
TLC R_f = 0.28 (CH_2Cl_2/MeOH 10%).

Quinoxaline (65)

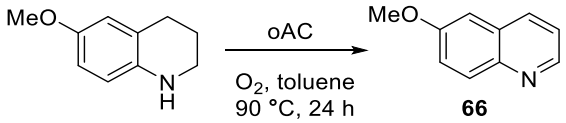


65

The general procedure was followed. 1,2,3,4-Tetrahydroquinoxaline (33.4 mg, 249 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 224 mg) and toluene (1.00 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7%, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 0% → 3%), which gave **65** (16 mg, 123 µmol, 49%) as a red oil. In a second reaction with oAC_{air} (n = 4.00, 224 mg) in toluene (1.00 mL), a yield of 67 % (22 mg, 169 µmol) was obtained. Spectroscopic data matches with recorded literature values.[177]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.87 (s, 2H, 2 x C*H*), 8.14-8.12 (m, 2H, 2 x C*H*), 7.81-7.78 (m, 2H, 2 x C*H*).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 145.1, 143.2, 130.2, 129.7.
HRMS (**ESI$^+$**) *m/z* calculated for $C_8H_7N_2$ $(M+H)^+$: 131.0604, found: 131.0605.
TLC R_f = 0.31 (CH_2Cl_2/MeOH 2%).

6-Methoxyquinoline (66)



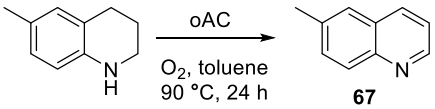
66

The general procedure was followed. 6-Methoxy-1,2,3,4-tetrahydroquinoline (40.8 mg, 250 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.00, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 0% → 10%), which gave **66** (33.8 mg, 212 µmol, 85 %) as a yellow oil. In a second reaction, an

NMR-yield of 91 % was obtained. Spectroscopic data matches with recorded literature values.[172] An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 72 % **66**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.77 (dd, ^3J = 4.2 Hz, ^4J = 1.6 Hz, 1H, C*H*), 8.03 (dd, ^3J = 8.3 Hz, ^3J = 1.2 Hz, 1H, C*H*), 8.00 (d, ^4J = 9.1 Hz, 1H, C*H*), 7.38-7.33 (m, 2H, 2 x C*H*), 7.06 (d, ^4J = 2.8 Hz, 1H, C*H*), 3.93 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 157.8, 148.1, 144.6, 134.9, 131.0, 129.4, 122.4, 121.5, 105.2, 55.7.
TLC R_f = 0.49 (CH_2Cl_2/MeOH 5 %).

6-Methylquinoline (67)

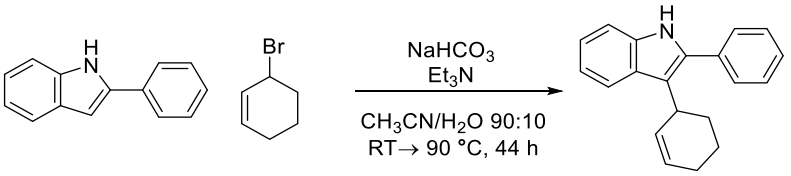


67

The general procedure was followed. 1,2,3,4-Tetrahydro-6-mehtylquinoline (36.6 mg, 249 µmol, 1.00 eq), $oAC_{air(\Delta)}$ (n = 4.00, 224 mg) and toluene (1.50 mL) were placed in a reaction tube under oxygen atmosphere. It was stirred for 24 h at 90 °C. The reaction was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH (7 %, 400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (CH_2Cl_2/MeOH 1.5 % → 2 %), which gave **67** (32.6 mg, 228 µmol, 92 %) as a yellow oil. Spectroscopic data matches with recorded literature values.[172] An additional control test was run in the same conditions for 30 minutes. The yield was determined with NMR as 65 % **67**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.85 (dd, ^3J = 4.3 Hz, ^4J = 1.7 Hz, 1H, C*H*), 8.06 (d, ^3J = 8.4 Hz, 1H, C*H*), 8.00 (d, ^3J = 8.5 Hz, 1H, C*H*), 7.57 (s, 1H, C*H*), 7.54 (dd, ^3J = 8.5 Hz, ^4J = 1.9 Hz, 1H, C*H*), 7.35 (dd, ^3J = 8.2 Hz, ^3J = 4.2 Hz, 1H, C*H*), 2.54 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 149.6, 147.0, 136.5, 135.5, 131.9, 129.3, 128.5, 126.7, 121.2, 21.7.
TLC R_f = 0.47 (CH_2Cl_2/MeOH 5 %).

2-Phenyl-3-(1-cyclohexen-3-yl)-indole (68.a)



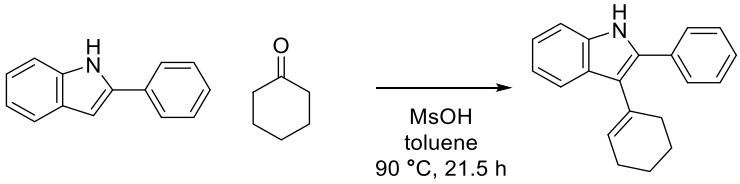
68.a

The synthesis was performed according to a modified procedure of WESTERMAIER *et al*.[178] 3-Bromocyclohexene (0.69 mL, 6.00 mmol, 1.20 eq) was added to a suspension of 2-phenylindole (966 mg, 5.00 mmol, 1.00 eq) and sodium bicarbonate (840 mg, 10.0 mmol, 2.00 eq) in acetonitrile/dist. H_2O (9:1, 25.0 mL). The reaction was stirred at r.t. and the pH of the reaction solution was monitored. Sodium bicarbonate (840 mg, 10.0 mmol, 2.00 eq) was added after 50 min and

trimethylamine (0.69 mL, 5.00 mmol, 1.00 eq) after 4 h. After stirring for 20 h at r.t. the reaction was refluxed for 1.5 h at 60 ˚C followed by 22 h at 90 ˚C. The reaction was then cooled to r.t. and, sequentially, dist. H_2O (2.5 mL), HCl aq. (1 M, 5 mL) and dist. H_2O (30 mL) were added. The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic phases were dried over $MgSO_4$. Flash chromatography (pentane/EtOAc 60:1 → 30:1) gave **68.a** (234 mg, 0.86 mmol, 17%) as pale-yellow solid.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.11 (s, 1H, N*H*), 7.60-7.48 (m, 5H, 5 x C*H*), 7.42-7.33 (m, 2H, 2 x C*H*), 7.43 (ddd, ^3J = 8.2 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H, C*H*), 6.94 (ddd, ^3J = 8.0 Hz, ^3J = 7.1 Hz, ^4J = 1.2 Hz, 1H, C*H*), 5.86-5.80 (m, 1H, CH_{Cy}), 5.67 (d, ^3J = 10.0 Hz, 1H, CH_{Cy}), 3.77-3.68 (m, 1H, CH_{stereo}), 2.27-1.87 (m, 5H, 2 x CH_2, 1 x C*H*H), 1.71-1.56 (m, 1H, 1 x C*H*H).
^{13}C-NMR (101 MHz, DMSO-d_6): δ = 136.3, 134.2, 133.0, 132.0, 2 x 128.6, 2 x 128.4, 127.4, 127.2, 126.5, 121.1, 120.0, 118.2, 114.9, 111.3, 33.1, 30.4, 24.5, 22.5.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{20}H_{20}N$ $(M+H)^+$: 274.1590, found: 274.1582.
TLC R_f = 0.47 (hexane/EtOAc 4:1).

2-Phenyl-3-(1-cyclohexen-1-yl)-indole (68.b)

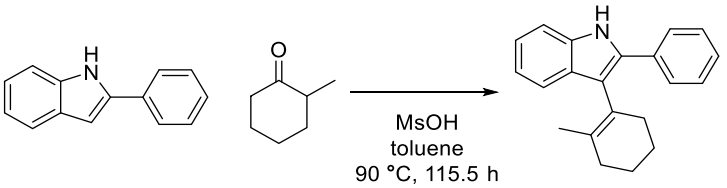


68.b

Cyclohexanone (248 µL, 2.40 mmol, 1.20 eq) and methanesulfonic acid (2.58 µL, 0.04 mmol, 0.02 eq) were added to a solution of 2-phenylindole (386 mg, 2.00 mmol, 1.00 eq) in toluene (4.00 mL). The reaction was stirred at 90 °C for 21.5 h and poured into $NaHCO_3$ (aq.) sature (20 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL), after which the combined organic phases were washed with dist. H_2O (20 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure, giving **68.b** (375 mg, 1.37 mmol, 69%) as a pale-yellow solid.

^{1}H-NMR (500 MHz, DMSO-d_6) δ = 7.70-7.68 (m, 2H, 2 x C*H*), 7.48-7.44 (m, 3H, 3 x C*H*), 7.36 (d, ^3J = 8.0 Hz, 1H, C*H*), 7.33-7.30 (m, 1H, C*H*), 7.10 (ddd, ^3J = 8.0 Hz, ^3J = 7.0 Hz, ^4J = 1.1 Hz, 1H, C*H*), 6.99 (ddd, ^3J = 7.9 Hz, ^3J = 7.0 Hz, ^4J = 0.9 Hz, 1H, C*H*), 5.78-5.77 (m, 1H, CH_{Cy}), 2.29-2.19 (s, 2H, CH_2), 2.13-2.09 (m, 2H, CH_2), 1.71-1.67 (m, 4H, 2 x CH_2).
^{13}C-NMR (126 MHz, DMSO-d_6) δ = 135.9, 133.1, 132.6, 131.8, 128.5 (2 x *C*H), 128.2, 127.1, 2 x 127.1, 126.7, 121.6, 2 x 119.0, 116.0, 111.1, 29.3, 25.3, 22.9, 21.9.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{20}H_{10}N$ $(M+H)^+$: 274.1590, found: 274.1584

2-Phenyl-3-(2-methyl-cylohexene-1-yl)-indole (68.c)

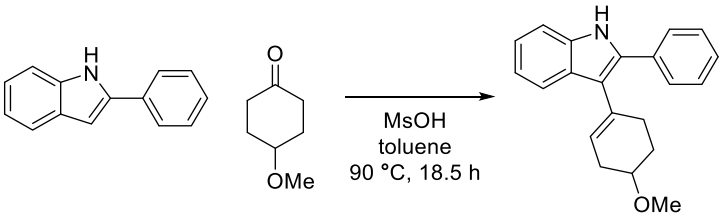


68.c

MsOH (5.03 µL, 77.5 µmol, 0.05 eq) was added into a solution of 2-methylcyclohexanone (227 µL, 1.86 mmol, 1.20 eq) and 2-phenylindole (300 mg, 1.55 mmol, 1.00 eq) in 5.00 mL toluene. The reaction was refluxed at 90 °C for 115.5 h, cooled to r.t. and poured into $NaHCO_3$ (aq.) sature (30 mL). The aqueous phase was extracted with CH_2Cl_2 (1 x 40 mL, 3 x 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and crude product was purified via flash chromatography (pentane/EtOAc 50:1), which gave **68.c** (70.9 mg, 247 µmol, 16%) as a pale-yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 1H, N*H*), 7.66-7.64 (m, 2H, 2 x C*H*), 7.44-7.37 (m, 4H, 4 x C*H*), 7.29 (ddd, ^3J = 7.4 Hz, ^3J = 1.8 Hz, ^4J = 1.8 Hz, 1H, C*H*), 7.20 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H, C*H*), 7.11 (ddd, ^3J = 8.0 Hz, ^3J = 7.1 Hz, ^4J = 1.1 Hz, 1H, C*H*), 2.27-2.05 (m, 4H, 2 x CH_2), 1.81-1.62 (m, 4H, 2 x CH_2), 1.49 (s, CH_3).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 136.0, 133.6, 132.7, 132.6, 129.1, 2 x 128.9, 127.3, 2 x 126.3, 124.8, 122.4, 120.2, 119.8, 117.3, 110.8, 31.8, 31.0, 24.0, 23.5, 21.0.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{22}H_{21}N$ $(M+H)^+$: 288.1747, found: 288.1747.
TLC R_f = 0.42 (hexane/EtOAc 4:1).

2-Phenyl-3-(4-methoxy-cylohexene-1-yl)-indole (68.d)

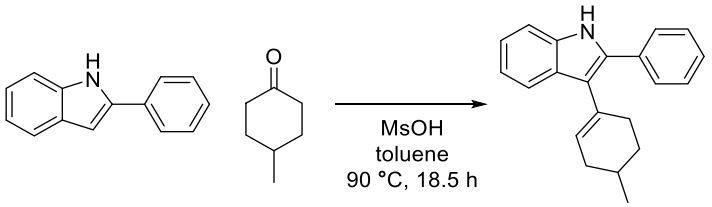


68.d

MsOH (5.03 µL, 77.5 µmol, 0.05 eq) was added to a solution of 4-methoxycyclohexanone (304 µL, 2.33 mmol, 1.50 eq) and 2-phenylindole (300 mg, 1.55 mmol, 1.00 eq) in 5.00 mL toluene. The reaction was refluxed at 90 °C for 18.5 h, during which the solution turned red. The reaction mixture was cooled to r.t. and poured into $NaHCO_3$ (aq.) sature (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL, 1 x 40 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and crude product was purified via flash chromatography (pentane/EtOAc 50:1 → 5:1), which gave **68.d** (396 mg, 1.31 mmol, 84%) as a pale-yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.31 (s, 1H, N*H*), 7.70-7.67 (m, 2H, 2 x C*H*), 7.48-7.43 (m, 3H, 3 x C*H*), 7.37-7.20 (m, 2H, 2 x C*H*), 7.10 (ddd, ^3J = 8.2 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, C*H*), 7.00 (ddd, ^3J = 7.9 Hz, ^3J = 6.9 Hz, ^4J = 1.0 Hz, 1H, C*H*), 5.66 (s, 1H, C*H*), 3.62-3.56 (m, 1H, CH*H*), 3.32 (s, 3H, CH_3), 2.57-2.51 (m, 1H, CH*H*), 2.26-2.21 (m, 3H, CH_2, CH*H*), 1.99-1.91 (m, 1H, CH*H*), 1.72-1.63 (m, 1H, CH*H*).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 135.9, 132.9, 132.7, 131.7, 2 x 128.5, 128.1, 127.2, 2 x 127.1, 124.0, 121.7, 119.1, 119.0, 115.2, 111.2, 74.5, 55.1, 31.4, 27.5, 27.4.
HRMS (**ESI**$^+$) *m/z* calculated for $C_{21}H_{21}NO$ $(M+H)^+$: 304.1696, found: 304.1681.
TLC R_f = 0.33 (hexane/EtOAc 4:1).

2-Phenyl-3-(4-methyl-cylohexene-1-yl)-indole (68.e)

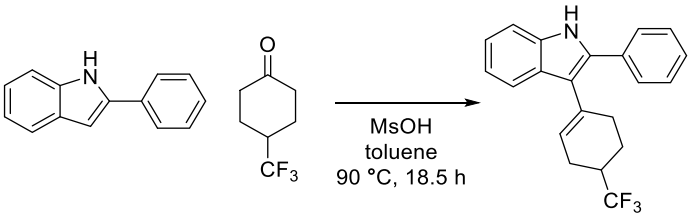


68.e

MsOH (5.03 µL, 77.5 µmol, 0.05 eq) was added to a solution of 4-methylcyclohexanone (287 µL, 2.33 mmol, 1.50 eq) and 2-phenylindole (300 mg, 1.55 mmol, 1.00 eq) in 5.00 mL toluene. The reaction was refluxed at 90 °C for 18 h, during which the solution turned red. The reaction mixture was cooled to r.t. and poured into $NaHCO_3$ (aq.) sature (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL, 1 x 40 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and crude product was purified via flash chromatography (pentane/EtOAc 50:1 → 20:1), which gave **68.e** (311 mg, 1.08 mmol, 70%) as a pale-yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.28 (s, 1H, N*H*), 7.69-7.66 (m, 2H, 2 x C*H*), 7.48-7.43 (m, 3H, 3 x C*H*), 7.37-7.29 (m, 2H, 2 x C*H*), 7.09 (ddd, ^3J = 8.1 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, C*H*), 6.99 (ddd, ^3J = 7.9 Hz, ^3J = 7.0 Hz, ^4J = 1.0 Hz, 1H, C*H*), 5.74 (s, 1H, C*H*), 2.33-2.08 (m, 3H), 1.89-1.71 (m, 3H), 1.41-1.31 (m, 1H, CH*H*), 1.02 (d, ^3J = 6.2 Hz, 3H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 135.9, 133.1, 132.6, 131.5, 2x 128.5, 128.2, 127.1, 2 x 127.1, 126.3, 121.6, 119.0, 118.9, 115.7, 111.1, 33.9, 31.0, 29.1, 27.7, 21.7.
HRMS (**ESI**$^+$) *m/z* calculated for $C_{21}H_{21}N$ $(M+H)^+$: 288.1747, found: 288.1741.
TLC R_f = 0.58 (hexane/EtOAc 4:1).

2-Phenyl-3-(4-trifluoromethyl-cylohexene-1-yl)-indole (68.f)

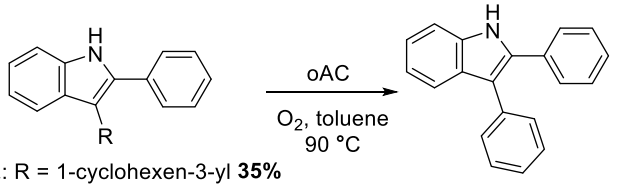


68.f

MsOH (5.03 µL, 77.5 µmol, 0.05 eq) was added into a solution of 4-trifluoromethylcyclohexanone (317 µL, 2.33 mmol, 1.50 eq) and 2-phenylindole (300 mg, 1.55 mmol, 1.00 eq) in 5.00 mL toluene. The reaction was refluxed at 90 °C for 17 h, cooled to r.t. and poured into $NaHCO_3$ (aq.) sature (30 mL). The aqueous phase was extracted with CH_2Cl_2 (1 x 40 mL, 2 x 30 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and crude product was purified via flash chromatography (pentane/EtOAc 40:1 → 10:1), which gave **68.f** (387 mg, 1.13 mmol, 73%) as a pale-yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.35 (s, 1H, N*H*), 7.68-7.65 (m, 2H, 2 x C*H*), 7.52-7.44 (m, 3H, 3 x C*H*), 7.38-7.31 (m, 2H, 2 x C*H*), 7.11 (ddd, ^3J = 8.0 Hz, ^3J = 7.0 Hz, ^4J = 1.1 Hz, 1H, C*H*), 7.01 (ddd, ^3J = 7.9 Hz, ^3J = 7.1 Hz, ^4J = 0.9 Hz, 1H, C*H*), 5.77 (s, 1H, C*H*), 2.74-2.60 (m, 1H, CH*H*), 2.48-2.43 (m, 1H, CH*H*), 2.34-2.17 (m, 3H), 2.01-1.96 (m, 1H, CH*H*), 1.68-1.58 (m, 1H, CH*H*).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 151.8, 140.2, 136.5, 132.0, 128.3, 127.7, 121.1, 120.5, 119.1, 113.0, 112.1, 37.5, 3 x 28.9.
^{19}F-NMR (400 MHz, DMSO-d_6) δ = 71.5.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{22}H_{18}F_3N$ (M+H)$^+$: 324.1464, found: 324.1464.
TLC R_f = 0.41 (hexane/EtOAc 4:1).

2,3-Diphenylindole (69.a = 69.b)



68.a: R = 1-cyclohexen-3-yl **35%**
68.b: R = 1-cyclohexen-1-yl **13 %**

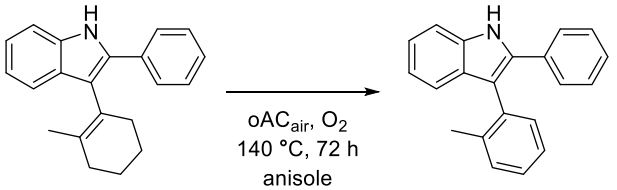
69.a = 69.b

In two separate reactions, 2-Phenyl-3-(1-cyclohexen-3-yl)-indol (**68.a**, 50.0 mg, 180 µmol, 1.00 eq) or 2-Phenyl-3-(1-cyclohexen-1-yl)-indol (**68.b**, 68.3 mg, 250 µmol, 1.00 eq), oAC_{HNO3} (n = 4.00, 164 mg **68.a,** 224 mg **68.b**) and toluene (1.00 mL) were placed in a reaction tube under an oxygen atmosphere. The reactions were stirred at 90 °C for 23 h (**68.a**) /73.5 h (**68.b**). The reaction mixture were cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2 (100 mL). The solvent was removed under reduced pressure and the crude product purified via flash chromatography (pentane/EtOAc 100:1 → 50:1), giving **69.a/b** (9 mg, 33.4 µmol, 13% from **68.b** 17 mg, 63.1 µmol, 35% from **68.a**) as a yellow oil. In a second reaction with with **68.a**

(68.5 mg, 251 mmol, 1.00 eq, 24 h reaction time) or **68.b** (68.0 mg, 249 mmol, 1.00 eq, 72 h reaction time) with oAC_{air} (n = 4.00, 224 mg) in toluene (1.50 mL), NMR-yields of 61% **69.a** as well as 49% **69.b** were obtained. Spectroscopic data matches with recorded literature values.[179]

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.24 (s, 1H, N*H*), 7.70-7.68 (m, 1H, C*H*), 7.46-7.23 (m, 12H, 12 x C*H*), 7.16 (ddd, ^3J = 8.1 Hz, ^3J = 6.9 Hz, ^4J = 1.1 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, $CDCl_3$) δ = 136.1, 135.2, 134.2, 132.9, 2 x 130.3, 2 x 128.8, 2 x 128.7, 2 x 128.3, 127.8, 126.4, 124.3, 122.9, 120.6, 119.9, 115.3, 111.0.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{20}H_{16}N$ $(M+H)^+$: 270.1277, found: 270.1279.
TLC R_f = 0.51 (Hexane/EtOAc 4:1).

2-Phenyl-3-(*o*-tolyl)-indole (69.c)

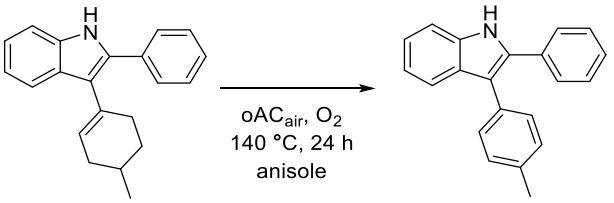


68.c **69.c**

The standard procedure was followed with **68.c** (64.1 mg, 223 µmol, 1.00 eq) and oAC_{air} (200 mg, n = 4.00) in anisole (1.34 mL). The reaction was stirred at 140 °C for 72 h. It was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH 12% (400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (pentane/EtOAc 50:1), which gave **69.c** (36.5 mg, 129 µmol, 58%) as a yellow oil. Spectroscopic data matches with recorded literature values.[180]

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.55 (s, 1H, N*H*), 7.46 (d, ^3J = 8.2 Hz, 1H, C*H*), 7.40-7.37 (m,2H, 2 x C*H*), 7.34-7.20 (m, 7H, 7 x C*H*), 7.15 (ddd, ^3J = 8.0 Hz, ^3J = 6.9 Hz, ^4J = 1.2 Hz, 1H, C*H*), 7.09 (d, ^3J = 7.9 Hz, 1H, C*H*), 6.98 (ddd, ^3J = 8.0 Hz, ^3J = 6.9 Hz, ^4J = 1.0 Hz, 1H, C*H*), 1.94 (s, 1H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 136.9, 136.0, 134.9, 133.6. 132.7, 131.2, 130.2, 128.7, 128.5 (2 x *C*H), 127.2, 127.1, 126.6 (2 x *C*H), 126.0, 121.9, 119.4, 118.7, 113.0, 111.4, 19.8.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{21}H_{18}N$ $(M+H)^+$: 284.1434, found: 284.1427.
TLC R_f = 0.42 (hexane/EtOAc 4:1).

2-Phenyl-3-(*p*-tolyl)-indole (69.e)

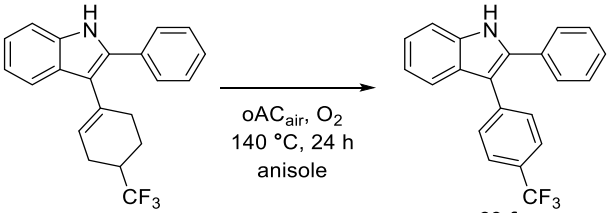


68.e **69.e**

The standard procedure was followed with **68.e** (71.9 mg, 250 µmol, 1.00 eq) and oAC$_{air}$ (224 mg, n = 4.00) in anisole (1.50 mL). The reaction was stirred at 140 °C for 24 h. It was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH 12% (400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (pentane/EtOAc 50:1 → 40:1), which gave **69.e** (51.0 mg, 180 µmol, 72%) as an orange oil. Spectroscopic data matches with recorded literature values.[180]

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.50 (s, 1H, N*H*), 7.47-7.42 (m, 4H, 4 x C*H*), 7.38-7.34 (m, 2H, 2 x C*H*), 7.31-7.27 (m, 1H, C*H*), 7.24-7.19 (m, 4H, 4 x C*H*), 7.15 (ddd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H, C*H*), 7.02 (ddd, ^3J = 7.9 Hz, ^3J = 7.0 Hz, ^4J = 1.0 Hz, 1H, C*H*), 2.34 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 136.1, 135.1, 133.8, 132.6, 132.2, 129.6, 129.3, 128.5, 128.1, 127.4, 121.9, 119.6, 118.6, 113.2, 111.4, 20.8.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{21}H_{18}N$ $(M+H)^+$: 284.1434, found: 284.1421.
TLC R_f = 0.49 (hexane/EtOAc 4:1).

2-Phenyl-3-(4-trifluoromethylphenyl)-indole (69.f)



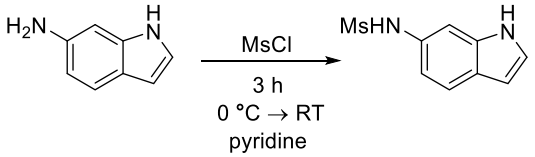
68.f **69.f**

The standard procedure was followed with **68.f** (85.2 mg, 250 µmol, 1.00 eq) and oAC$_{air}$ (224 mg, n = 4.00) in anisole (1.50 mL). The reaction was stirred at 140 °C for 24 h. It was cooled to 0 °C, filtered through a pad of celite and washed with CH_2Cl_2/MeOH 12% (400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography (pentane/EtOAc 40:1), which gave **69.f** (68.8 mg, 204 µmol, 65 %) as an adduct with 1.00 eq EtOAc as a yellow oil. Spectroscopic data matches with recorded literature values.[181]

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.73 (s, 1H, N*H*), 7.74-7.72 (m, 2H, 2 x C*H*), 7.58-7.54 (m, 3H, 3 x C*H*), 7.49-7.33 (m, 6H, 6 x C*H*), 7.20 (ddd, ^3J = 8.1 Hz, ^3J = 6.9 Hz, ^4J = 1.1 Hz, 1H, C*H*), 7.09 (ddd, ^3J = 8.0 Hz, ^3J = 7.0 Hz, ^4J = 1.0 Hz, 1H, C*H*).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 136.1, 135.1, 133.8, 132.6, 132.2, 129.6, 129.3, 128.5, 128.1, 127.4, 121.9, 119.6, 118.6, 113.2, 111.4, 20.8.

^{19}F-NMR (377 MHz, DMSO-d_6): δ = 60.2.
TLC R_f = 0.35 (hexane/EtOAc 4:1).

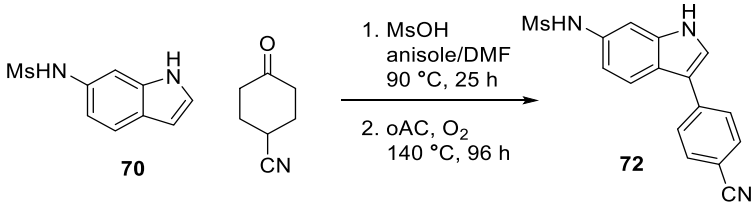
N-(1*H*-Indol-6-yl)-methanesulfonamide (70)



A procedure of Yudasaka et al. was followed.[182] MsCl (293 µL, 3.78 mmol, 1.00 eq) was added to a stirred solution of 6-aminoindole (500 mg, 3.78 mmol, 1.00 eq) in toluene (20.0 mL) at 0 °C. Upon heating to r.t., the solution turned red. After stirring at r.t. for 3 h pyridine was removed under reduced pressure. Dist. H_2O (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (4 x 20 mL). The combined organic phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and crude product was purified via flash chromatography for three times (CH_2Cl_2/MeOH 1 → 2%, 1 → 1.5%, 0.5 → 1%), giving **70** (507 mg, 2.41 mmol, 64%) as a pale-yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.05 (s, 1H, N*H*), 9.38 (s, 1H, N*H*), 7.47 (d, ^3J = 8.4 Hz, 1H, C*H*), 7.32-7.39 (m, 2H, 2 x C*H*), 6.90 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1H, C*H*), 6.38 (s, 1H, C*H*), 2.88 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 136.0, 132.0, 125.5, 125.0, 120.4, 114.2, 104.3, 100.9, 38.4.
HRMS (**ESI**$^+$) *m/z* calculated for $C_9H_{10}N_2NaO_2S$ $(M+Na)^+$: 233.0355, found: 233.0365.
TLC R_f = 0.33 (CH_2Cl_2/MeOH 10 %).

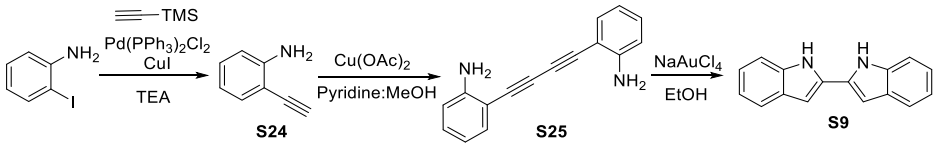
N-(1*H*-3-(4-Cyanophenyl)-indol-6-yl)-methanesulfonamide (72)



MsOH (2.39 µL, 36.9 µmol, 0.05 eq) was added to a stirred solution of **70** (155 mg, 737 µmol, 1.00 eq) and 4-oxocyclohexanecarbonitrile (172 µL, 1.47 mmol, 2.00 eq) in anisole/DMF (2.50 mL, 4:1). The reaction was stirred at 90 °C for 25 h. oAC (330 mg) was added to the reaction mixture and it was stirred at 140 °C under oxygen atmosphere for another 96 h. It was cooled to r.t., filtered through a pad of celite and washed with CH_2Cl_2/MeOH 12% (400 mL). The solvent was removed under reduced pressure and crude product was purified via flash chromatography twice (CH_2Cl_2/MeOH 0 → 5%, 1%), which gave **72** (94.5 mg, 304 µmol, 41%) as a yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 11.62 (s, 1H, N*H*), 9.57 (s, 1H, N*H*), 7.93 (d, ^3J = 2.7 Hz, 1H, C*H*), 7.91-7.87 (m, 3H, 3 x C*H*), 7.85-7.82 (m, 2H, 2 x C*H*), 7.40 (d, ^4J = 1.7 Hz, 1H, C*H*), 7.05 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1H, C*H*), 2.93 (s, 3H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 140.8, 137.5, 133.0, 2 x 132.7, 2 x 126.3, 125.9, 121.7, 119.7, 119.4, 115.0, 114.0, 107.0, 104.3, 38.6.
HRMS (**ESI**$^+$) *m/z* calculated for $C_{16}H_{13}N_3NaO_2S$ $(M+Na)^+$: 334.0621, found: 334.0615.
TLC R_f = 0.49 (CH_2Cl_2 10:1).

1H,1'H-2,2'-Biindole (S9)



The synthesis of 1H,1'H-2,2'-Biindole was carried out in 3 steps:[98]
(a) 2-iodoaniline (2.64 g, 12.1 mmol), $Pd(PPh_3)_2Cl_2$ (50.6 mg, 72.1 µmol) and CuI (32.7 mg, 17.1 µmol) were loaded into a dry flask under Ar atmosphere. The flask was degassed and refilled with Ar (3 times). TEA (40 mL) and TMS-acetylene (1.8 mL, 12.6 mmol) were injected. The reaction was stirred for 20 h at r.t. The reaction was quenched with EtOAc and TEA was extracted with saturated NH_4Cl (aq.) (2 times). The organic phase was dried with $MgSO_4$ and evaporated. The crude product was dissolved in MeOH (100 mL) and K_2CO_3 was added and the mixture was stirred for 30 min. The solvent was partially evaporated and salt was precipitated with the addition of nHex. The solution was then filtered and the solvents were evaporated. Product was purified with flash column chromatography using EtOAc:nHex (1:6) as eluent. Yield of **S24** was 1.38 g, 98%.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 (d, J = 7.6 Hz, 1H), 7.14 (dd, J = 8.2, 7.3 Hz, 1H), 6.75 – 6.62 (m, 2H), 3.38 (s, 1H).

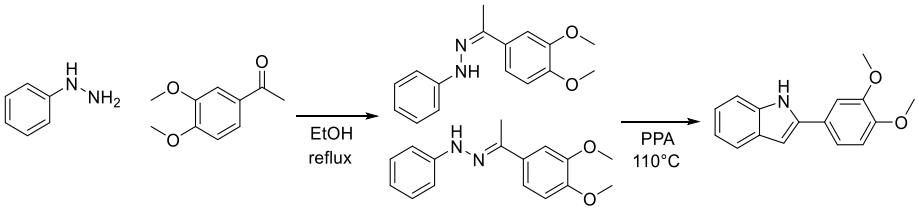
(b) $Cu(OAc)_2$*H_2O (3.66 g, 18.3 mmol) was loaded in to a flask and dissolved in pyridine:MeOH (1:1) (20 mL) and **S24** (1.08 g, 9.19 mmol) was added. The reaction was stirred for 5.5 h at r.t. The reaction was quenched with H_2O and the crude product was extracted with Et_2O. The organic phase was dried with $MgSO_4$ and evaporated. The product was purified with flash column chromatography using EtOAc:nHex (1:8 -> 1:4 -> 1:2) as eluent. Yield of **S25** was 0.942 g, 88%.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.22 (d, J = 7.7 Hz, 2H), 7.11 (dd, J = 8.6, 7.1 Hz, 2H), 6.71 (d, J = 8.2 Hz, 2H), 6.52 (dd, J = 7.5 Hz, 2H), 5.62 (s, 4H).

(c) Compound **S25** (0.325 g, 1.40 mmol) and $NaAuCl_4$*$2H_2O$ (24.1 mg, 60.6 µmol) were loaded in to a flask and degassed and refilled with Ar. EtOH (11 mL) was degassed with Ar bubbling for 30 min and then injected in to the flask. The flask was covered with Al foil to protect it from light and stirred at r.t. for 3.5 h. Solvents were evaporated and the products were separated by recrystallization from EtOAc and nHex. Yield of **S9** was 1.93 g, 59%.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.51 (s, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.11 (dd, 2H), 7.00 (dd, 2H), 6.91 (s, 2H).

2-(3,4-Dimethoxyphenyl)-1H-indole (S10)



1-(3,4-Dimethoxyphenyl)ethanone (0.89 g, 5.0 mmol) and phenylhydrazine (0.5 mL, 5.1 mmol) were dissolved in EtOH abs. (20 mL) and heated up to reflux in a dean-stark system, and every 30 minutes the 10 mL EtOH accumulated was substituted with new EtOH absolute. After 2 h the solvent was evaporated in a rotavapor and kept under vacuum for 1 h. The crude intermediate solid product was then crushed into small pieces.

PPA (18 mL) was added and the mixture was heated up to 110°C in an oil bath. The reaction was kept under mechanical stirring for 1 h before quenching with H_2O.

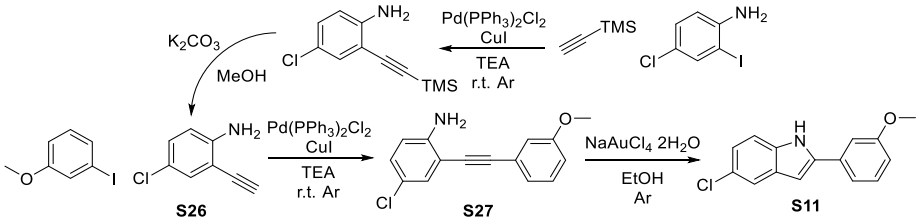
The liquid phase was poured slowly in an Erlenmeyer flask with $NaHCO_3$ (aq.) sature and more $NaHCO_3$ (aq.) sature was used to clean completely the reaction flask and to completely neutralize the mixture.

The solid precipitate was filtered and cleaned with H_2O and dried under vacuum. More product was extracted from the liquid phase with DCM, evaporated and kept under vacuum.

Product was recrystallized in DCM:nHex (1:1). Yield of **S10** was 0.49 g, 39%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 7.49 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.40 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.38 (s, 1H), 7.09 – 7.02 (m, 2H), 6.97 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.81 (dd, *J* = 2.2, 0.9 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H).

5-Chloro-2-(3-methoxyphenyl)-1H-indole (S11)



The synthesis of **S11** was carried out in 3 steps:

(a) 4-Chloro-2-iodoaniline (1.01 g, 4.0 mmol), $Pd(PPh_3)_2Cl_2$ (25.1 mg, 35.8 µmol) and CuI (14.1 mg, 74.0 µmol) were loaded into a dry flask, degassed and refilled with Ar (3 times). TEA (40 mL) previously refluxed under CaH_2 was added and reaction was stirred for 2h. Reaction was then quenched with EtOAc and cleaned from TEA through extractions with NH_4Cl (aq.). Organic phase was then filtered through a short

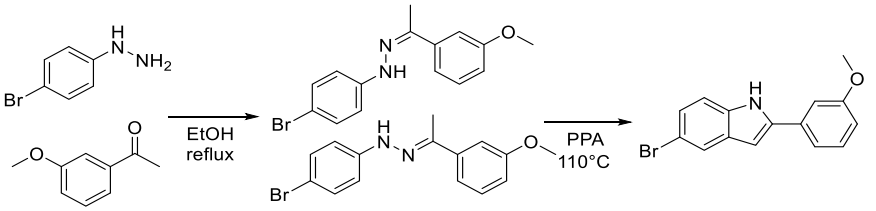
silica column with EtOAc as eluent and solvent was then evaporated almost completely until an oily solution was obtained. The crude oil was diluted in MeOH (70 mL) and 7 g of K_2CO_3 was added, and this second solution stirred for 2 h. Product was extracted with Et_2O and solvent evaporated obtaining 0.6040 g of crude product that was immediately used in the synthesis of **S26**.

(b) 0.6040 g of crude **S26**, $Pd(PPh_3)_2Cl_2$ (26.9 mg, 38.3 µmol) and CuI (15.6 mg, 82.0 µmol) were loaded into a dry flask, degassed and refilled with Ar (3 times). TEA (15 mL) previously refluxed under CaH_2 was added and reaction was stirred for 2.5 h. Reaction was then quenched with EtOAc, and cleaned from TEA through extractions with NH_4Cl (aq.). Organic phase was dried with $MgSO_4$, filtered and evaporated. Yield of **S27** was 0.88 g, 86%.

(c) **S27** (0.84 g, 3.2 mmol) and $NaAuCl_4$ (12.9 mg, 32.4 µmol) were dissolved in EtOH (20 mL). Solution was kept under stirring at r.t. for 2 h. Half of the solvent was evaporated in rotavapor before filtering through a short silica column with EtOAc as eluent. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:9->1:4) as eluent. Yield of **S11** was 0.80 g, 96%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.47 – 7.34 (m, 4H), 7.09 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.91 (dddd, *J* = 4.5, 3.6, 2.4, 1.2 Hz, 2H), 3.84 (s, 3H).
HRMS Calculated for $[C_{15}H_{12}ClNO+]$: 257.0607, found: 257.0609.

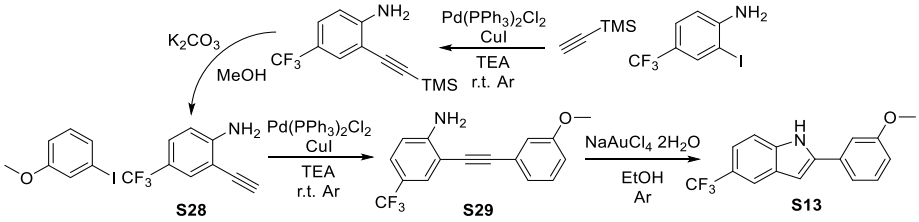
5-Bromo-2-(3-methoxyphenyl)-1H-indole (S12)



1-(3-Methoxyphenyl)ethanone (0.75 mL, 5.5 mmol) and 4-bromophenylhydrazine (1.2 g, 5.3 mmol) were dissolved in EtOH abs. (40 mL) and heated up to reflux in a dean-stark system. Every 30 minutes the 10 mL EtOH accumulated were substituted with new EtOH absolute. After 2 h the solvent was evaporated in a rotavapor and kept under vacuum for 1 h. The crude intermediate solid product was then crushed into small pieces. PPA (9 mL) was added and the mixture was heated up to 110°C in an oil bath. The reaction was kept under mechanical stirring for 20 minutes before quenching with H_2O.
The liquid phase was poured slowly in an Erlenmeyer flask with $NaHCO_3$ (aq.) sature and more $NaHCO_3$ (aq.) sature was used to clean the reaction flask and to completely neutralize the mixture. The solid precipitate was filtered and cleaned with H_2O and dried under vacuum. More product was extracted from the liquid phase with DCM, evaporated and kept under vacuum. Product was recrystallized in DCM:nHex (1:1). Yield of **S12** was 0.27 g, 19%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.46 – 7.34 (m, 4H), 7.20 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.93 – 6.89 (m, 2H), 3.84 (s, 3H).
HRMS Calculated for [$C_{15}H_{12}ClNO$+]: 301.0102, found: 301.0101.

2-(3-Methoxyphenyl)-5-(trifluoromethyl)-1H-indole (S13)



The synthesis of S12 was carried out in 3 steps:
(a) 2-Iodo-4-(trifluoromethyl)aniline (1.0 g, 3.5 mmol), $Pd(PPh_3)_2Cl_2$ (31.3 mg, 44.6 µmol) and CuI (13.9 mg, 73.0 µmol) were loaded into a dry flask, degassed and refilled with Ar (3 times). TEA (15 mL) previously refluxed under CaH_2 was added and reaction was stirred for 2h.
Reaction was then quenched with EtOAc, and cleaned from TEA through extractions with NH_4Cl (aq). Organic phase was then filtered through a short silica column with EtOAc as eluent and solvent was evaporated almost completely until an oily solution is obtained.
The crude oil was diluted in MeOH (50 mL) and 7 g of K_2CO_3 was added, and the resulting solution stirred for 2 h. Product was extracted with Et_2O and solvent evaporated obtaining 0.64 g of crude product that was immediately used in the synthesis of **S28**.

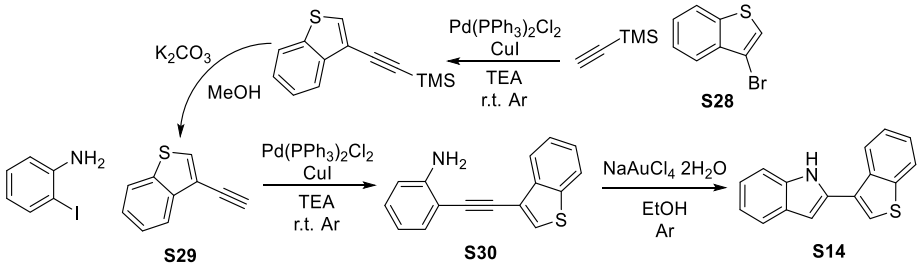
(b) 0.64 g of crude **S28**, $Pd(PPh_3)_2Cl_2$ (28.1 mg, 40.0 µmol) and CuI (13.2 mg, 69.3 µmol) were loaded into a dry flask, degassed and refilled with Ar (3 times). TEA (15 mL) previously refluxed under CaH_2 was added and reaction was stirred for 2.75 h. Reaction was then quenched with EtOAc, and cleaned from TEA through extractions with NH_4Cl (aq). Organic phase was dried with $MgSO_4$, filtered and evaporated. Yield of **S29** was 0.82 g, 82%.

(c) **S29** (0.66 g, 2.2 mmol) and $NaAuCl_4$(41.4 mg, 0.1 mmol) were dissolved in EtOH (20 mL). Solution was kept under stirring at 70°C for 2 h.
Half of solvent was evaporated in rotavapor before filtering through a short silica column with EtOAc as eluent.
Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:4) as eluent. Yield of **S13** was 0.63 g, 96%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.98 (s, 1H), 7.94 – 7.90 (m, 1H), 7.58 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.43 – 7.36 (m, 2H), 7.09 (dd, *J* = 2.2, 0.9 Hz, 1H), 6.94 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H), 3.85 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 159.79, 139.78, 138.50, 132.78, 130.11, 127.87, 125.54 (d, *J* = 271.2 Hz), 120.22 (q, *J* = 30.8 Hz), 117.90 (q, *J* = 3.1 Hz), 117.75, 117.55 (q, *J* = 4.2 Hz), 113.77, 111.93, 110.64, 99.84, 55.26.
HRMS Calculated for [$C_{16}H_{12}F_3NO$+]: 291.0871, found: 291.0880.

2-(Benzo[b]thiophen-3-yl)-1H-indole (S14)



The synthesis of S12 was carried out in 3 steps:
(a) **S28** (1.4 g, 6.7 mmol), $Pd(PPh_3)_2Cl_2$ (50.3 mg, 71.7 µmol) and CuI (19.9 mg, 0.10 mmol) were loaded into a dry flask, degassed and refilled with Ar (3 times). TEA (20 mL) previously refluxed under CaH_2 was added and reaction was stirred for 2h. Reaction was then quenched with EtOAc, and cleaned from TEA through extractions with NH_4Cl (aq). Organic phase was then filtered through a short silica column with EtOAc as eluent and solvent was evaporated almost completely until an oily solution was obtained.
The crude oil was diluted in MeOH (50 mL) and 7 g of K_2CO_3 were added, the resulting solution was stirred for 2 h. Product was extracted with Et_2O and solvent evaporated obtaining 0.36 g of crude **S20** that was immediately used in the synthesis of **S29**.

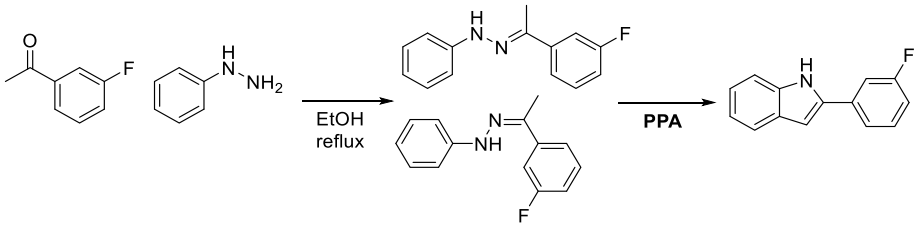
(b) 0.36 g of crude **S29**, $Pd(PPh_3)_2Cl_2$ (15.3 mg, 21.8 µmol) and CuI (8.3 mg, 43.6 µmol) were loaded into a dry flask, degassed and refilled with Ar (3 times). TEA (10 mL) previously refluxed under CaH_2 was added and reaction was stirred for 2.5 h.
Reaction was then quenched with EtOAc, and cleaned from TEA through extractions with NH_4Cl (aq). Organic phase was dried with MgSO4, filtered and evaporated. Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:19->1:9) as eluent. Yield overall of **S30** was 0.34 g, 18%.

(c) **S30** (0.34 g, 1.3 mmol) and $NaAuCl_4$ (22.9 mg, 57.6 µmol) were dissolved in EtOH (10 mL). Solution was kept under stirring at 70°C for 2 h. Half of solvent was evaporated in rotavapor before filtering through a short silica column with EtOAc as eluent.
Product was purified using flash column chromatography with silica as stationary phase and EtOAc:nHex (1:19->1:9) as eluent. Yield of **S14** was 0.24 g, 70%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.55 (s, 1H), 8.30 (dt, *J* = 8.1, 1.0 Hz, 1H), 8.11 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.05 (s, 1H), 7.62 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.54 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.48

(ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H), 7.44 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.05 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.95 (dd, *J* = 2.2, 0.9 Hz, 1H).

2-(3-Fluorophenyl)-1H-indole (S15)



1-(3-Fluorophenyl)ethanone (1.5 mL, 12.2 mmol) and phenylhydrazine (1.2 mL, 12.2 mmol) were dissolved in EtOH abs. (40 mL) and heated up to reflux in a dean-stark system. Every 30 minutes the 10 mL EtOH accumulated was substituted with new EtOH absolute. After 2 h the solvent was evaporated in a rotavapor and kept under vacuum for 1 h. The crude intermediate solid product was then crushed into small pieces.

PPA (20 mL) was added and the mixture was heated up to 110°C in an oil bath. The reaction was kept under mechanical stirring for 20 minutes before quenching with H_2O.

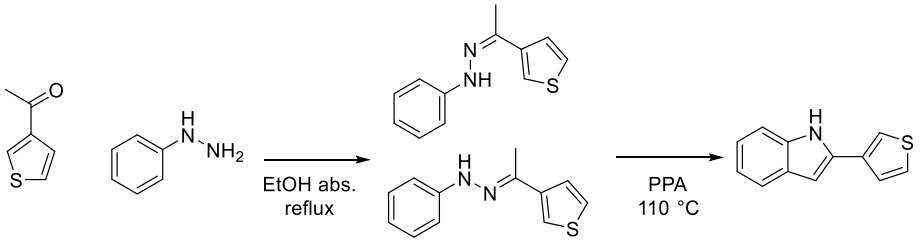
The liquid phase was poured slowly in an Erlenmeyer flask with $NaHCO_3$ (aq.) sature and more $NaHCO_3$ (aq.) sature was used to clean the reaction flask and to completely neutralize the mixture.

The solid precipitate was filtered and cleaned with H_2O and dried under vacuum. More product was extracted from the liquid phase with DCM, evaporated and kept under vacuum.

Product was recrystallized in DCM:nHex (2:1). Yield of **S15** was 0.59 g, 23%.

HRMS Calculated for $[C_{14}H_{10}FN+]$: 211.0797, found: 211.0810.

2-(thiophen-3-yl)-1H-indole (S16)



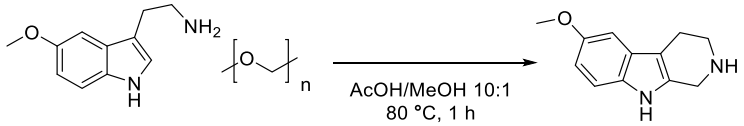
1-(thiophen-3-yl)ethan-1-one (1.4 g, 11.0 mmol) and phenylhydrazine (1.2 mL, 12.2 mmol) were dissolved in EtOH abs. (40 mL) and heated up to reflux in a dean-stark system, and every 30 minutes the 10 mL EtOH accumulated was substituted with new EtOH absolute. After 2 h the solvent was evaporated in a rotavapor and kept under vacuum for 1 h. The crude intermediate solid product was then crushed into small pieces. PPA (15 mL) was added and the mixture was heated up to 110°C in an

oil bath. The reaction was kept under mechanical stirring for 1 h before quenching with H_2O.

The liquid phase was poured slowly in an Erlenmeyer flask with $NaHCO_3$(aq) sature and more $NaHCO_3$(aq) sature was used to clean completely the reaction flask and to completely neutralize the mixture. The solid precipitate was filtered, cleaned with H_2O and dried under vacuum more product was extracted from the liquid phase with DCM, evaporated and kept under vacuum. Product was recrystallized in DCM:nHex (1:1). Yield of **S16** was 1.2 g, 53%.

^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 8.40 (s, 1H), 7.58 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.50 – 7.48 (m, 1H), 7.46 – 7.44 (m, 2H), 7.40 (dq, *J* = 8.1, 0.9 Hz, 1H), 7.17 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.71 (dd, *J* = 2.2, 1.0 Hz, 1H).

1,2,3,4-Tetrahydro-6-methoxy-1*H*-pyrido[3,4-*b*]indole (S17)



The reaction was performed according to a method of YE *et al*.[164] Paraformaldehyde (52.1 mg, 1.73 mmol, 1.10 eq) was added to a solution of 5-methoxytryptamine (300 mg, 1.58 mmol, 1.00 eq) in AcOH/MeOH (10:1, 1.10 mL). The reaction was stirred at 80 °C for 1 h under reflux cooling. After cooling to r.t., the solution was basified to a pH of 10 with $NH_3 \cdot H_2O$ (aq. 25%, 1.5 mL). Dist. H_2O (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL/1 x 20 mL). The combined organic phases were washed with brine (10 mL), which was then extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were again combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash chromatography (CH_2Cl_2/MeOH 10% → 17%), which gave **S17** (193 mg, 954 µmol, 60%) as a grey solid. Spectroscopic data matches with recorded literature values.[183]

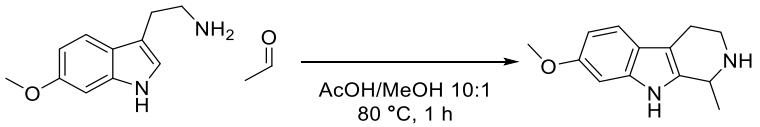
^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.44 (s, 1H, N*H*-9), 7.13 (d, ^3J = 8.6 Hz, 1H, C*H*-8), 6.84 (d, ^4J = 2.8 Hz, 1H, C*H*-5), 6.62 (dd, ^3J = 8.6 Hz, ^4J = 2.5 Hz, 1H, C*H*-7), 3.82 (s, 2H, CH_2-1), 3.73 (s, 3H, CH_3-10), 2.96 (t, ^3J = 5.6 Hz, 2H, CH_2-3), 2.56 (t, ^3J = 5.6 Hz, 2H, CH_2-4).

^{13}C-NMR (101 MHz, DMSO-d_6) δ = 152.9 (*C*-6), 134.9 (*C*-9a), 130.5 (*C*-8a), 127.6 (*C*-4b), 111.3 (*C*H-8), 109.6 (*C*H-7), 106.8 (*C*-4a), 99.6 (*C*H-5), 55.3 (*C*H_3-10), 43.4 (*C*H_2-3), 42.7 (*C*H_2-1), 22.2 (*C*H_2-4).

HRMS (**ESI$^+$**) *m/z* calculated for $C_{12}H_{15}N_2O$ $(M+H)^+$: 203.1179, found: 203.1184.

TLC R_f = 0.11 (CH_2Cl_2/MeOH 15 %).

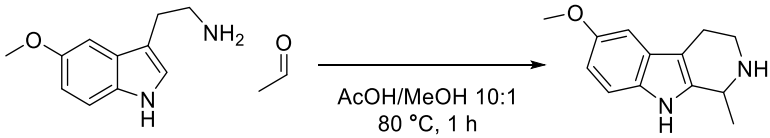
2,3,4,9-tetrahydro-1H-harmine (S18)



The reaction was performed according to a modified method of YE *et al*.[164] Acetaldehyde (44.6 µL, 789 µmol, 1.50 eq) was added to a solution of 6-methoxytryptamine (100 mg, 526 µmol, 1.00 eq) in AcOH/MeOH (10:1, 1.00 mL). The reaction was stirred at 80 °C for 1 h in a sealed tube. After cooling to r.t., the solution was basified to a pH of 10 with $NH_3 \cdot H_2O$ (aq. 25%, 1.5 mL). Dist. H_2O (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL, 1 x 10 mL). The combined organic phases were washed with brine (10 mL), which was then extracted with CH_2Cl_2 (2 x 10 mL). The organic phases were again combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash chromatography (CH_2Cl_2/MeOH 8% → 18%), which gave **S18** (103 mg, 476 µmol, 91%) as a pale-yellow solid. Spectroscopic data matches with recorded literature values.[184]

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.51 (s, 1H, N*H*), 7.21 (d, ^3J = 8.5 Hz, 1H, C*H*), 6.79 (d, ^4J = 2.9 Hz, 1H, C*H*), 6.59 (dd, ^3J = 8.4 Hz, ^4J = 2.2 Hz, 1H, C*H*), 4.01 (q, ^3J = 6.6 Hz, 1H, C*H*), 3,74 (s, 3H, CH_3), 3.15 (ddd, ^2J = 13.3 Hz, ^3J = 5.3 Hz, ^3J = 3.3 Hz, 1H, C*H*H), 2.87-2.80 (m, 1H, C*H*H), 2.62-2.52 (m, 2H, CH_2), 1.34 (d, ^3J = 6.6 Hz, 1H, CH_3).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 155.0, 136.5, 136.2, 121.5, 117.9, 107.7, 106.4, 94.6, 55.1, 47.8, 42.1, 22.2, 20.4.
HRMS (**ESI$^+$**) *m/z* calculated for $C_{13}H_{17}N_2O$ $(M+H)^+$: 217.1335, found: 217.1325.
TLC R_f = 0.37 (CH_2Cl_2/MeOH 15%).

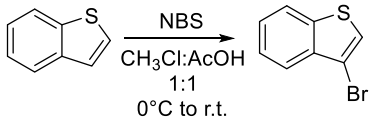
1,2,3,4-tetrahydro-isoharmine (S20)



The reaction was performed according to a method of YE *et al*.[164] Acetaldehyde (98.2 µL, 1.74 mmol, 1.10 eq) was added to a solution of 5-methoxytryptamine (300 mg, 1.58 mmol, 1.00 eq) in AcOH/MeOH (10:1, 1.10 mL). The reaction was stirred at 80 °C for 1 h under reflux cooling. After cooling to r.t., the solution was basified to a pH of 10 with $NH_3 \cdot H_2O$ (aq. 25%, 1.5 mL). Dist. H_2O (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL, 1 x 20 mL). The combined organic phases were washed with brine (10 mL), which was then extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were again combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified via flash chromatography (CH_2Cl_2/MeOH 5% → 17%), which gave **S20** (308 mg, 1.42 mmol, 90%) as a pale-yellow solid. Spectroscopic data matches with recorded literature values.[185]

^{1}H-NMR (400 MHz, DMSO-d_6) δ = 10.52 (s, 1H, N*H*-9), 7.15 (d, ^3J = 8.6 Hz, 1H, C*H*-8), 6.84 (d, ^4J = 2.6 Hz, 1H, C*H*-5), 6.64 (dd, ^3J = 8.6 Hz, ^4J = 2.5 Hz, 1H, C*H*-7), 4.05-4.00 (m, 1H, C*H*-1), 3.73 (s, 3H, CH_3-11), 3.27 (s, 1H, N*H*-2), 3.20-3.14 (m, 1H, CH_2-3), 2.88-2.82 (m, 1H, CH_2-3), 2.63-2.54 (m, 2H, CH_2-4), 1.35 (d, ^3J = 6.7 Hz, 3H, CH_3-10).
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 152.9 (*C*H-6), 138.6 (*C*-9a), 130.6 (*C*-8a), 127.3 (*C*-4b), 111.4 (*C*H-8), 109.9 (*C*H-7), 106.5 (*C*-4a), 99.8 (*C*H-5), 55.3 (*C*H_3-11), 48.0 (*C*H-1), 42.2 (*C*H_2-3), 22.2 (*C*H_2-4), 20.3 (*C*H_3-10).
HRMS (**ESI$^+$**) *m/z* calculated for $C_{13}H_{17}N_2O$ $(M+H)^+$: 217.1335, found: 217.1329.
TLC R_f = 0.11 (CH_2Cl_2/MeOH 15%).

3-bromobenzo[b]thiophene (S28)



Benzothiophene (1.0 g, 7.5 mmol) was dissolved ifn $CHCl_3$ and AcOH mixture (15 mL), NBS (1.6 g, 9.1 mmol) was added in 3 different additions through 1 h at 0°C and the solution is left heating up under UV lamp for 2 h. Reaction was quenched with NaS_2O_4(aq) 10% and $NaHCO_3$(aq) sature. Product was extracted with $CHCl_3$ and organic solution dried with $MgSO_4$, filtered and evaporated in a rotavapor and vacuum. The red solution obtained was filtered through a short silica column with cyclohexane as eluent. The yellow solution obtained was evaporated and a yellow oil obtained. Yield of **S28** was 1.5 g, 93%.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 – 7.81 (m, 2H), 7.48 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.45 (d, *J* = 0.4 Hz, 1H), 7.44 – 7.40 (m, 1H).

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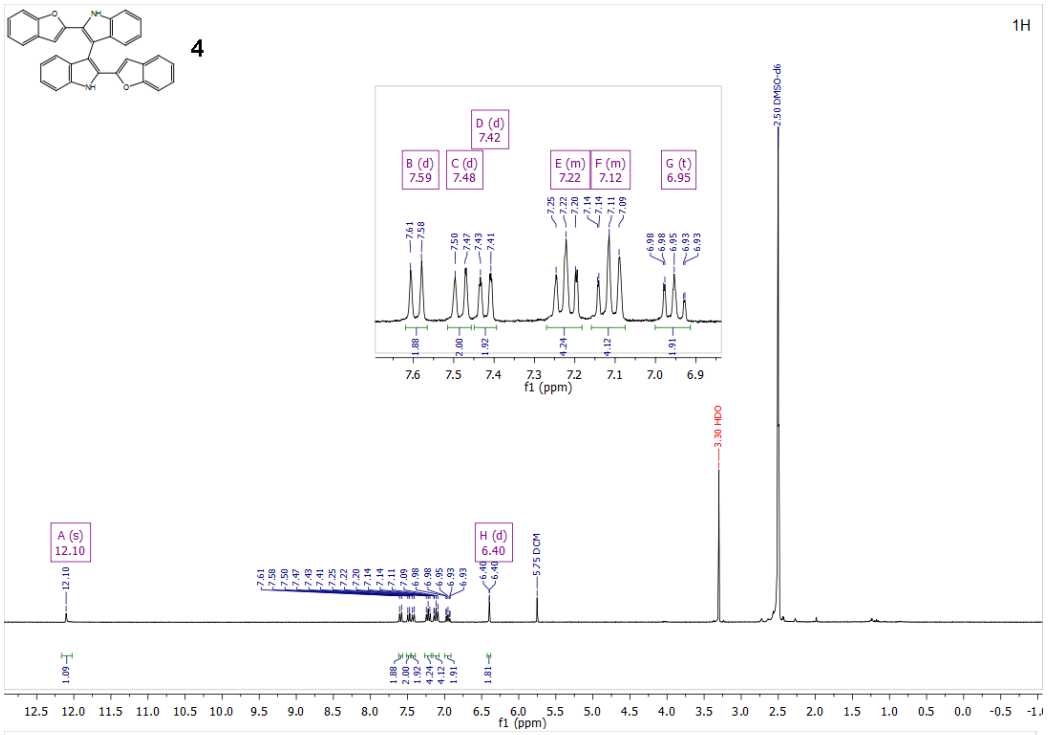
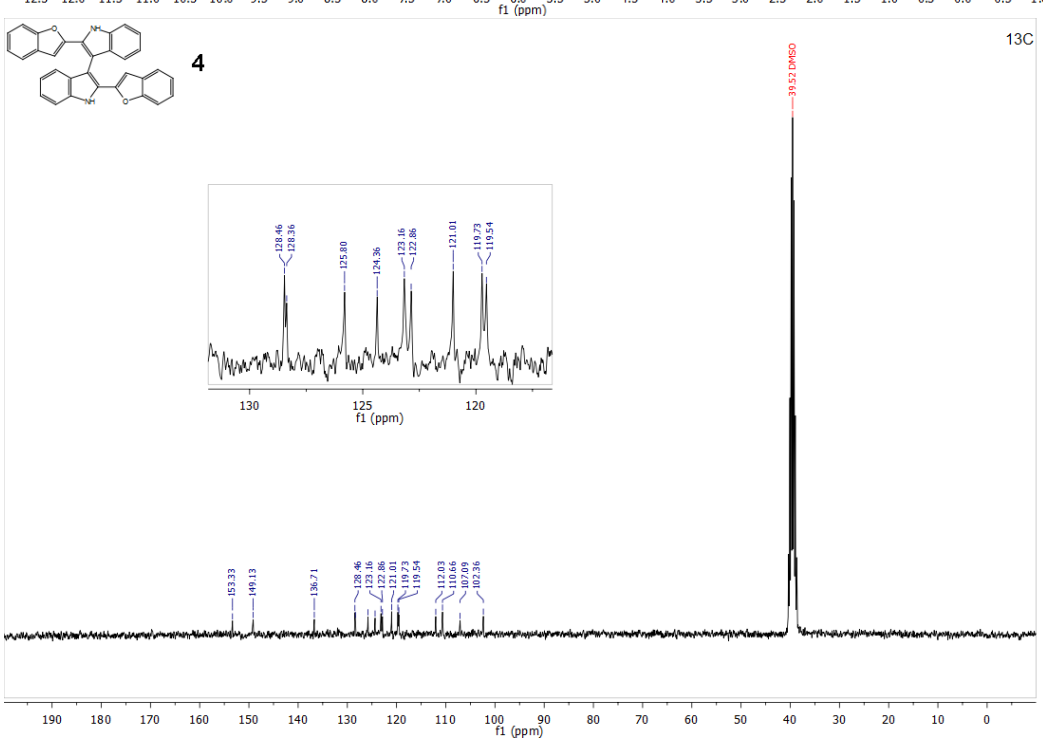
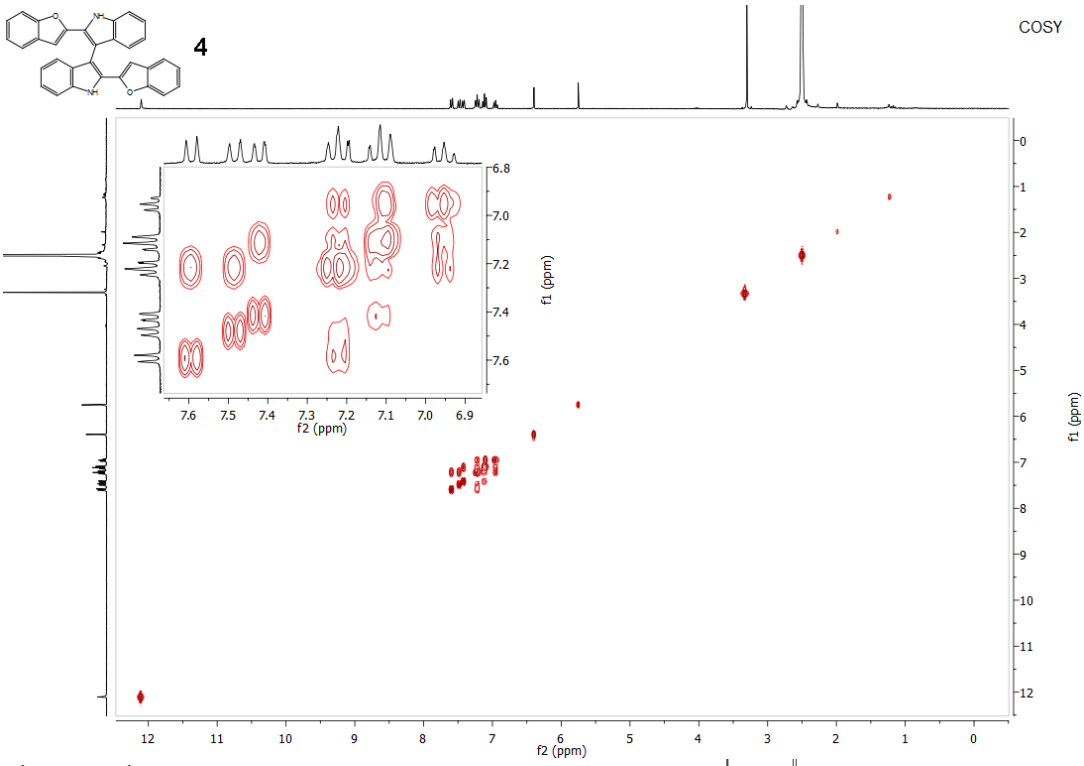
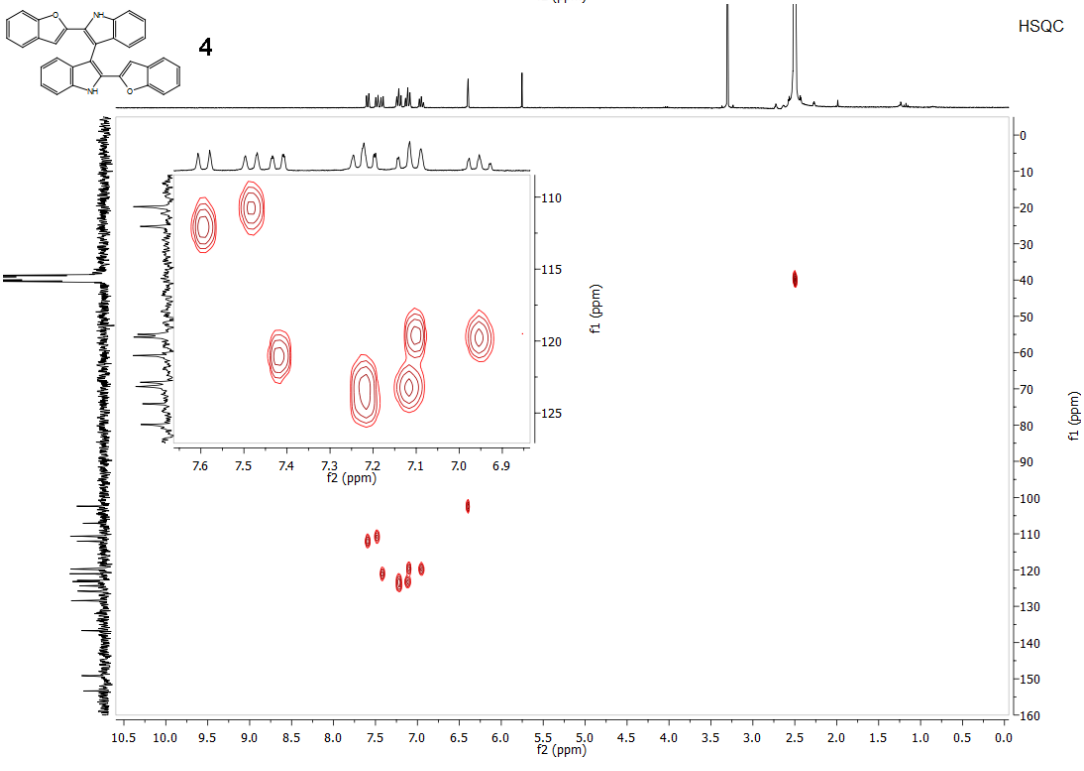
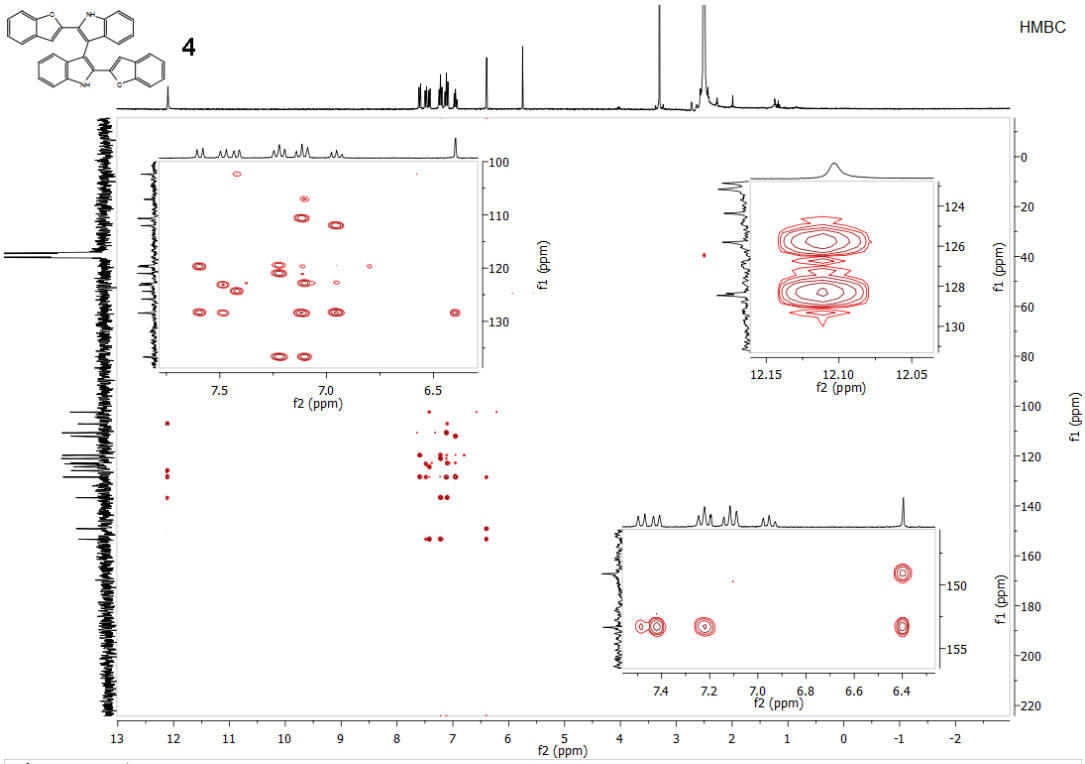
5 – APPENDIX

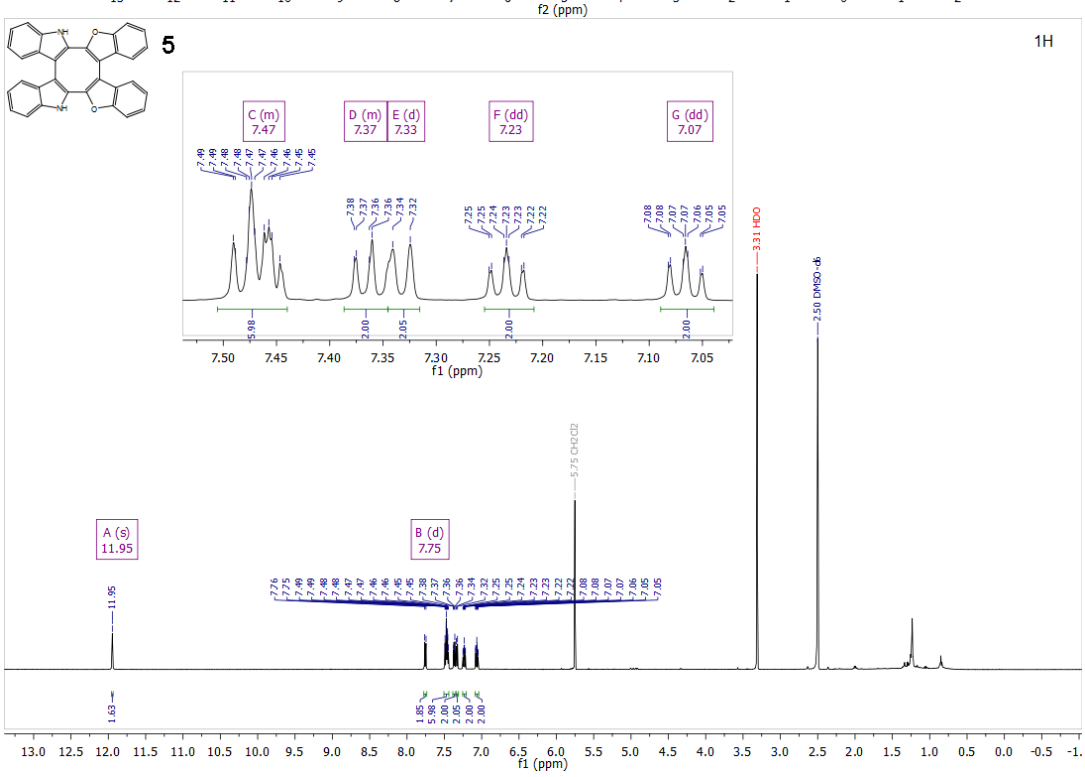

1H
4
A (s) 12.10
B (d) 7.59
C (d) 7.48
D (d) 7.42
E (m) 7.22
F (m) 7.12
G (t) 6.95
H (d) 6.40
2.50 DMSO-d6
3.30 HDO
5.75 DCM
f1 (ppm)


13C
4
39.52 DMSO
f1 (ppm)


4
COSY
f2 (ppm)
f1 (ppm)


4
HSQC
f2 (ppm)
f1 (ppm)


4
HMBC
f1 (ppm)
f2 (ppm)


5
1H
C (m) 7.47
D (m) 7.37
E (d) 7.33
F (dd) 7.23
G (dd) 7.07
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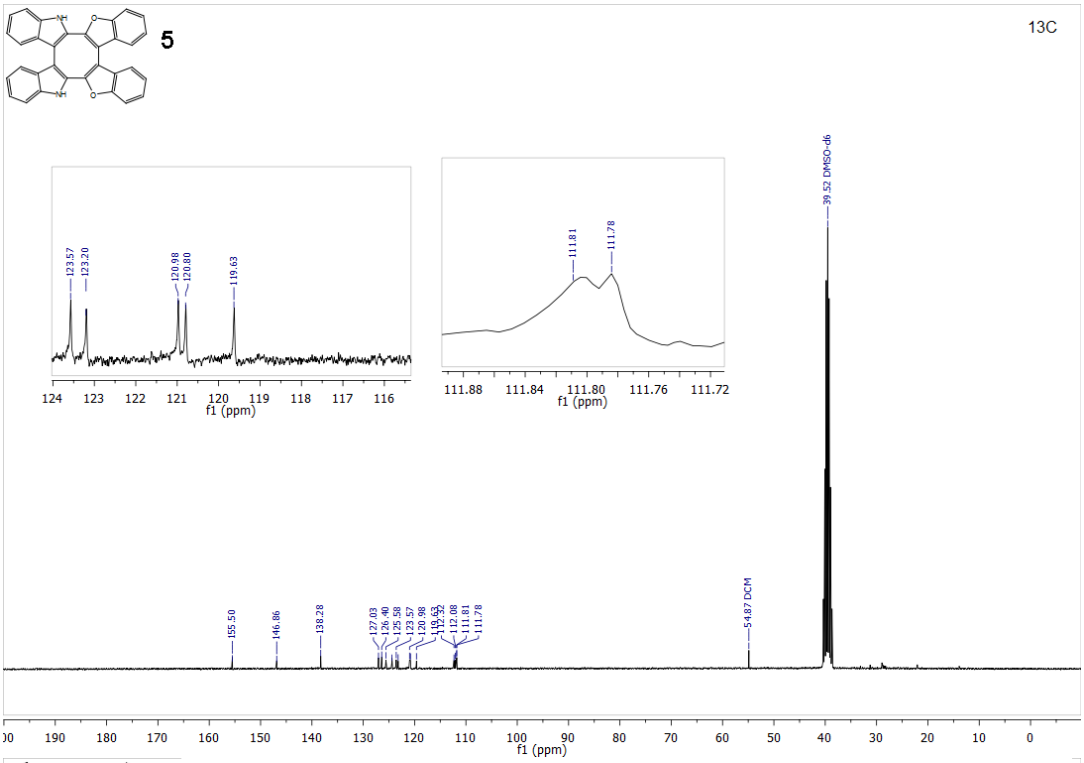
B (d) 7.75
3.31 HDO
2.50 DMSO-d6
5.75 CH2Cl2
f1 (ppm)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111.78
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138.28
127.03
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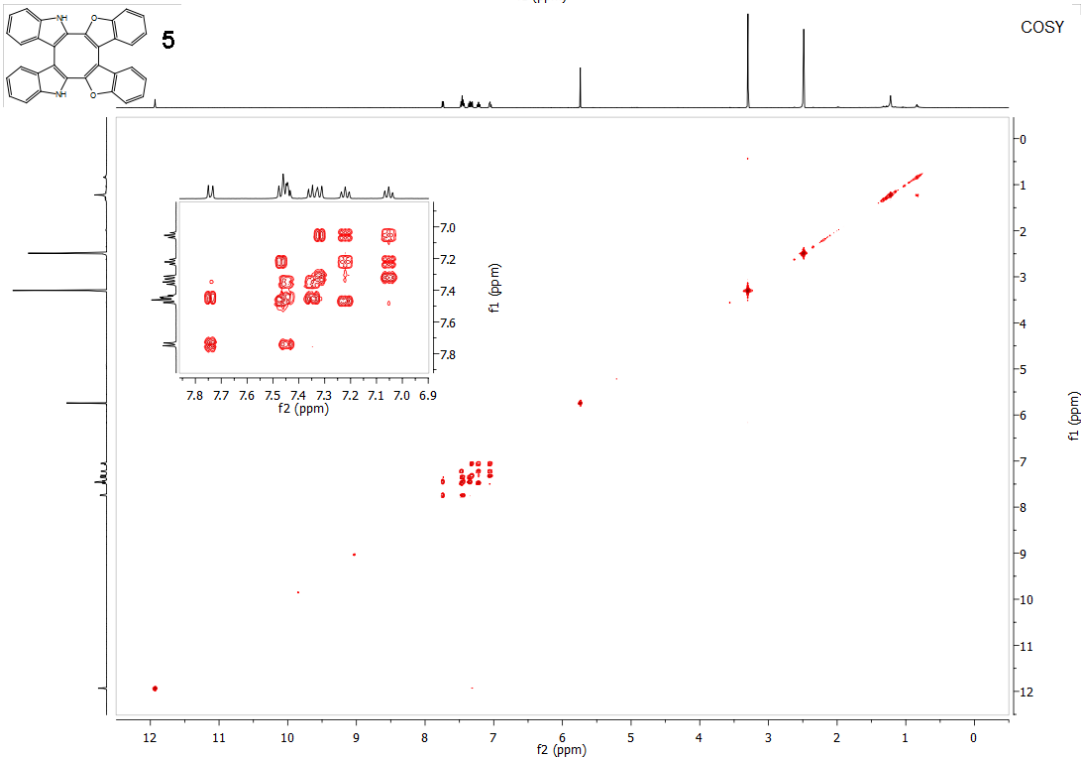
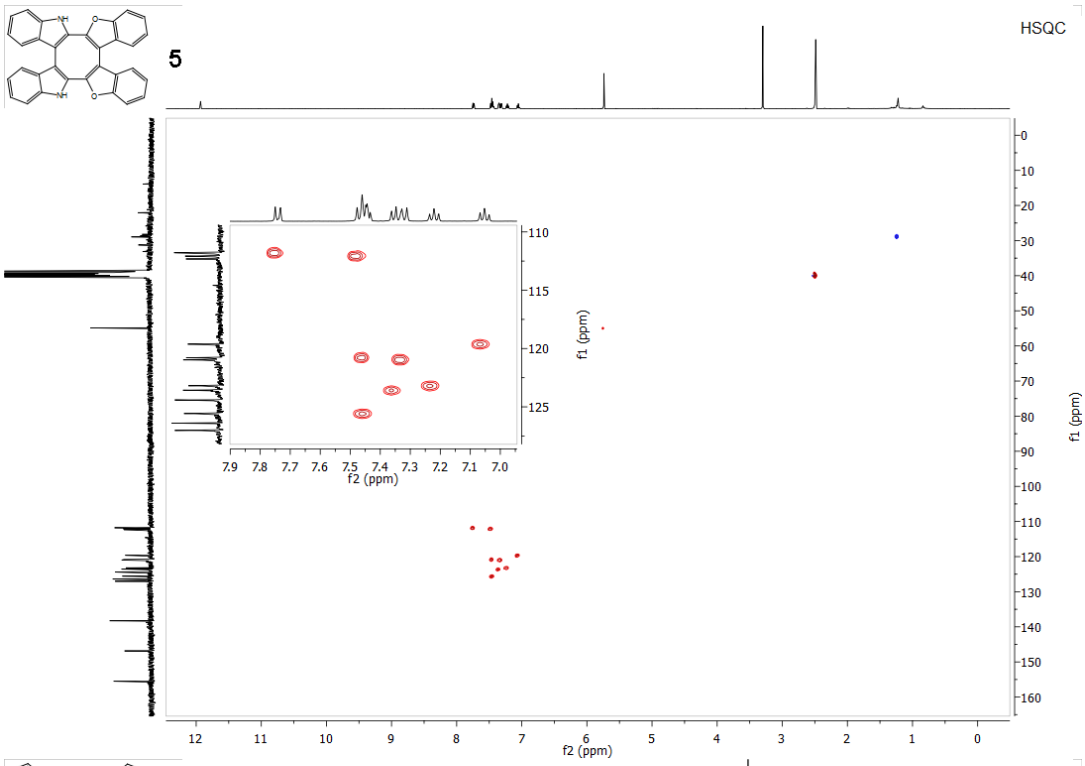
111.88
111.81
111.78
54.87 DCM
f1 (ppm)


5
COSY
f1 (ppm)
f2 (ppm)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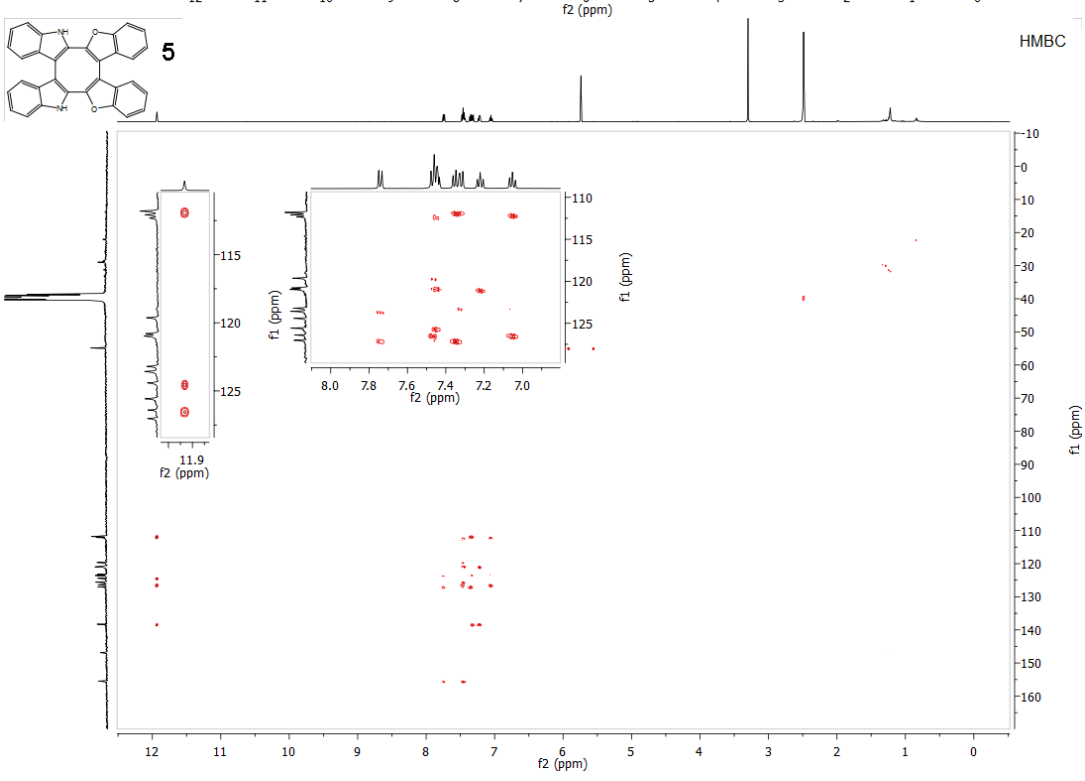
HSQC
f2 (ppm)
f1 (ppm)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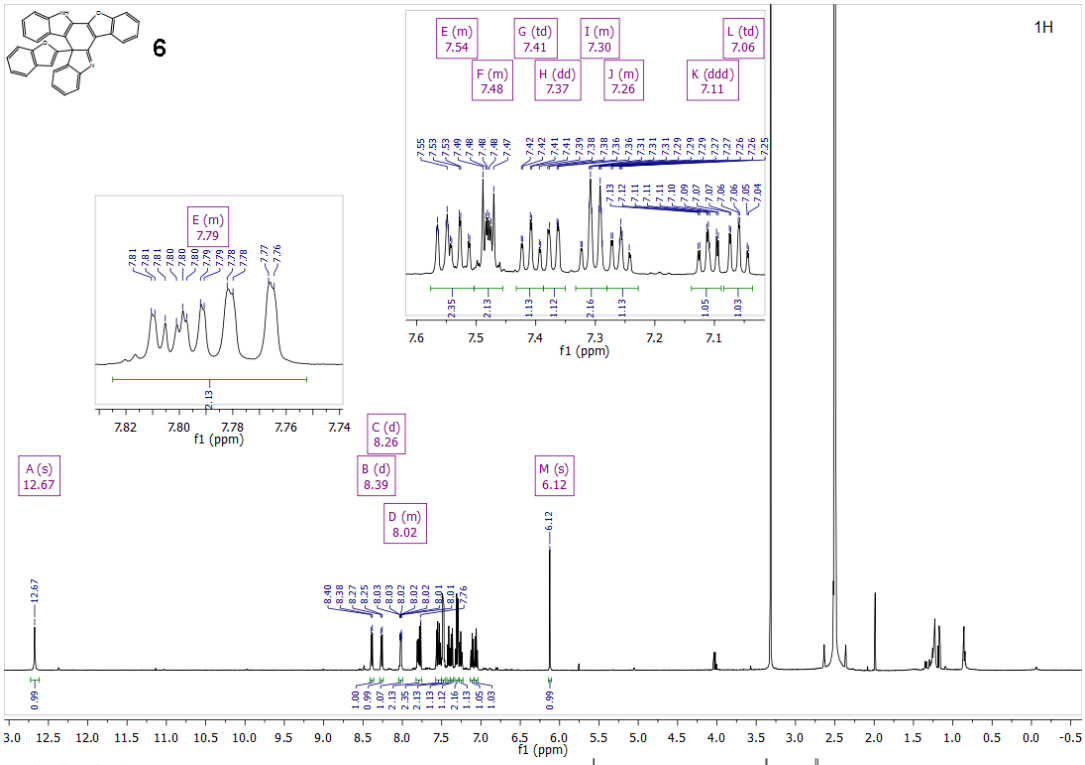
HMBC
f2 (ppm)
f1 (ppm)


6
1H
E (m)
7.54
G (td)
7.41
I (m)
7.30
L (td)
7.06
F (m)
7.48
H (dd)
7.37
J (m)
7.26
K (ddd)
7.11
E (m)
7.79
A (s)
12.67
C (d)
8.26
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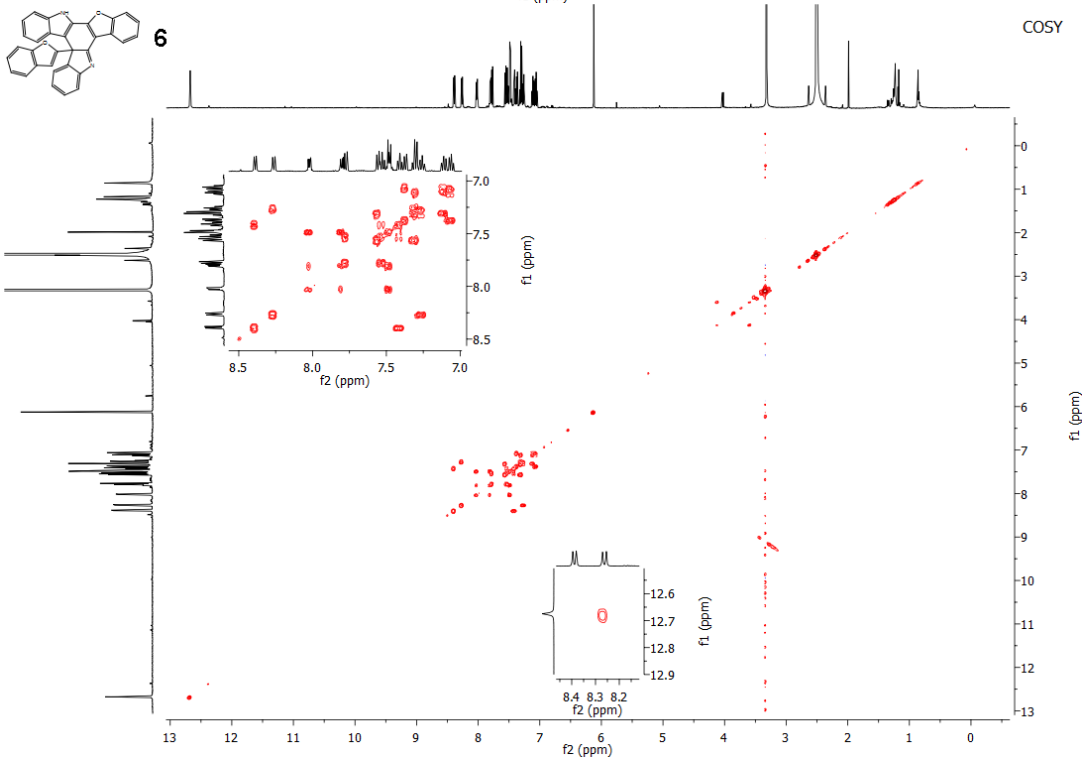
D (m)
8.02
M (s)
6.12
f1 (ppm)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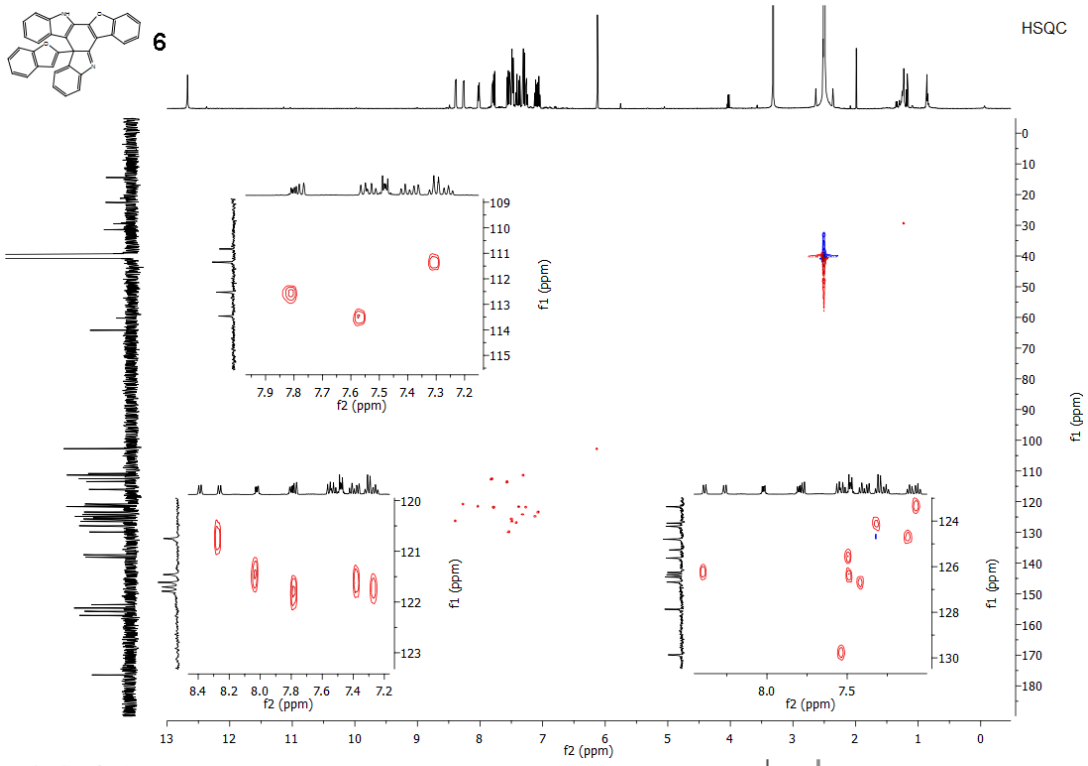
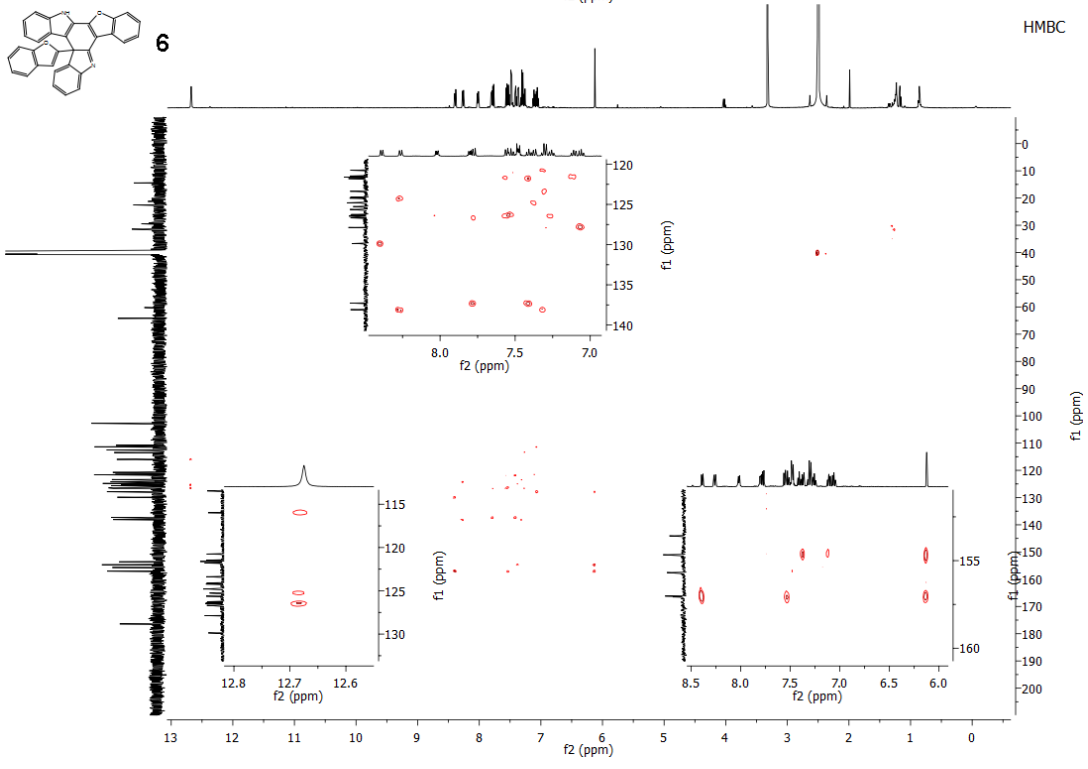
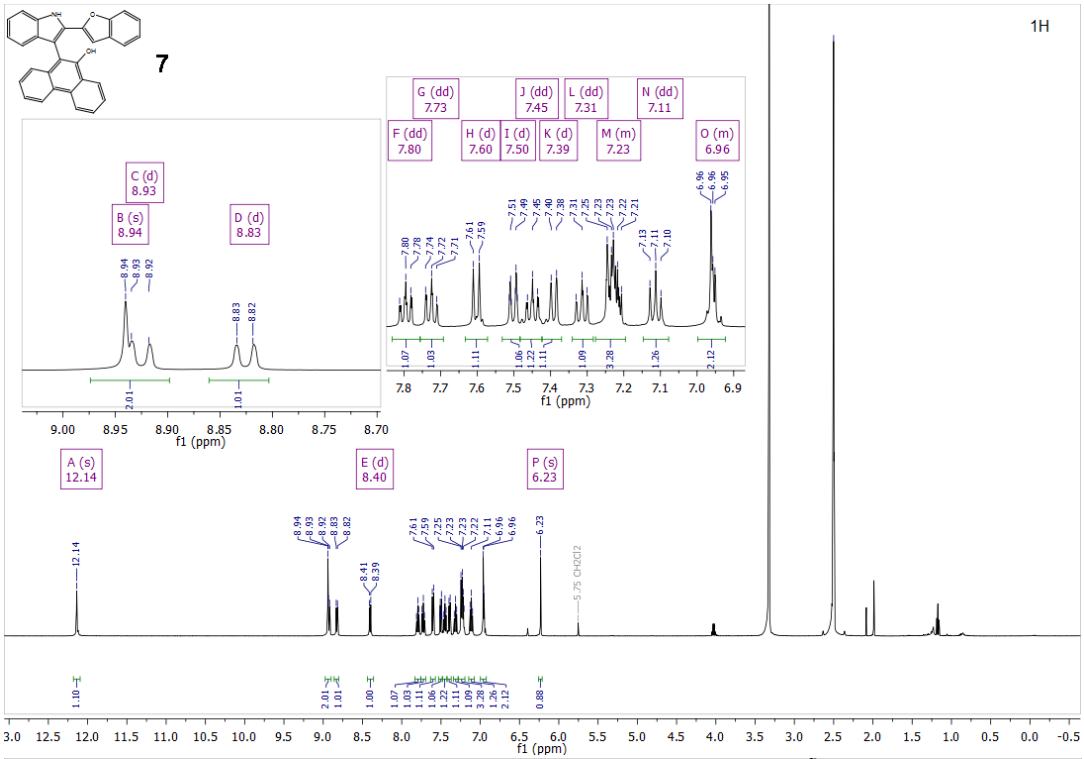
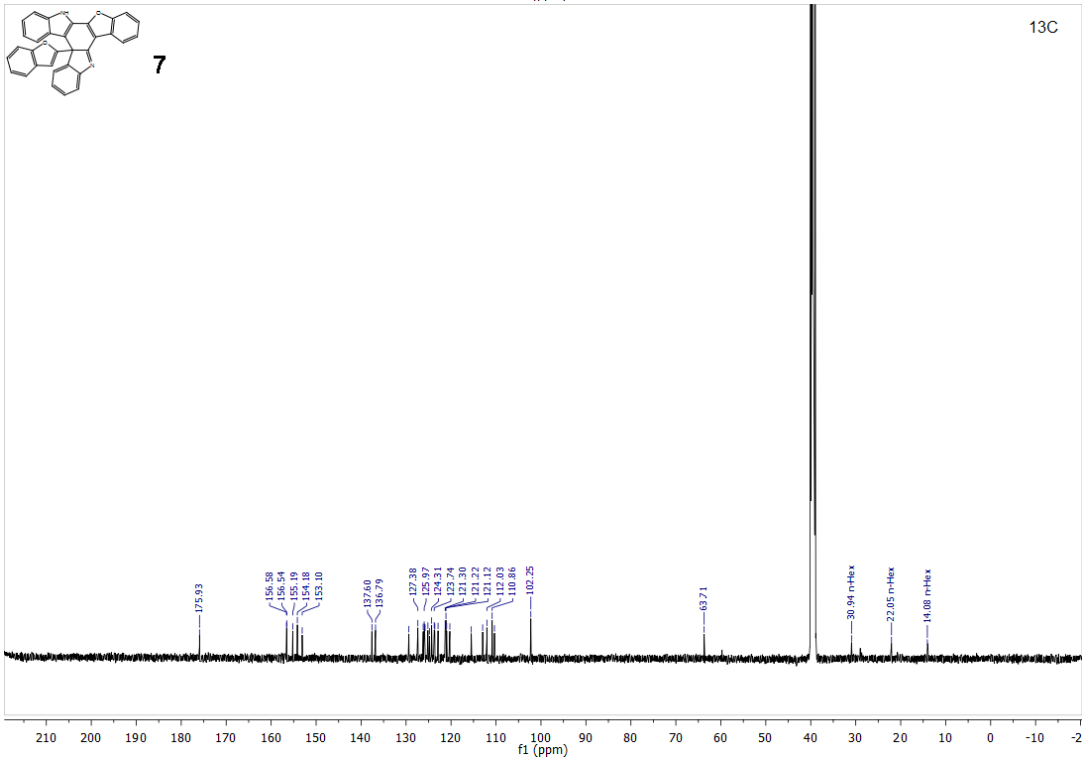
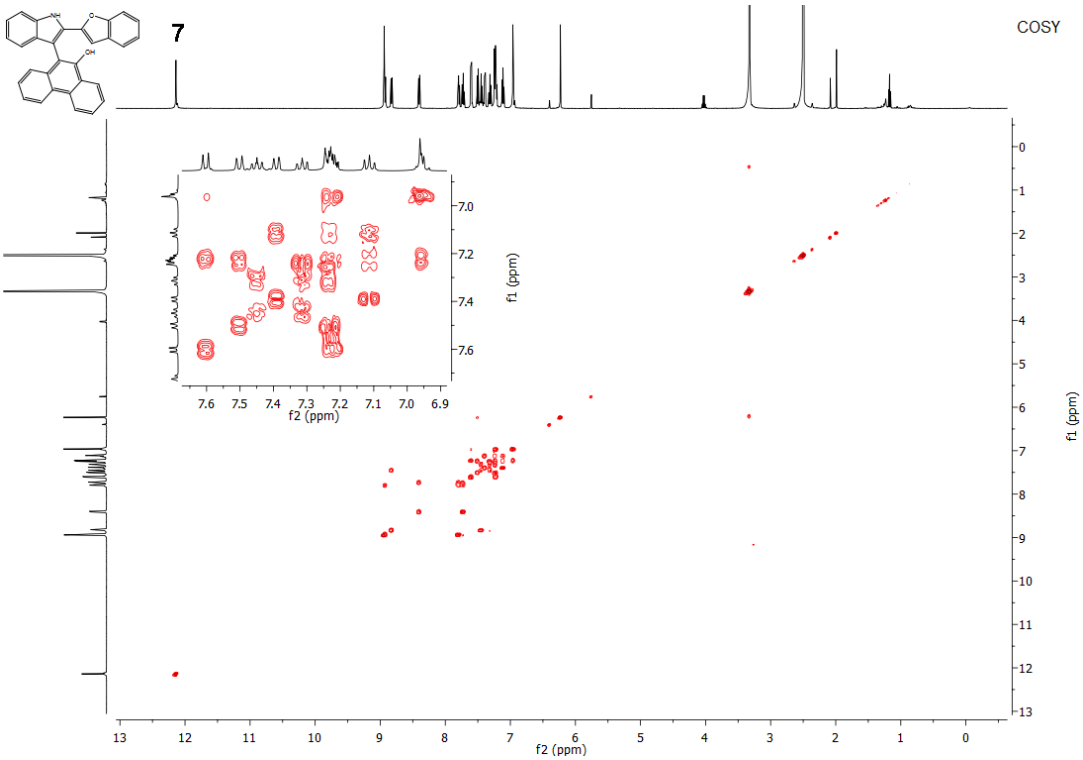
f1 (ppm)
f2 (ppm)

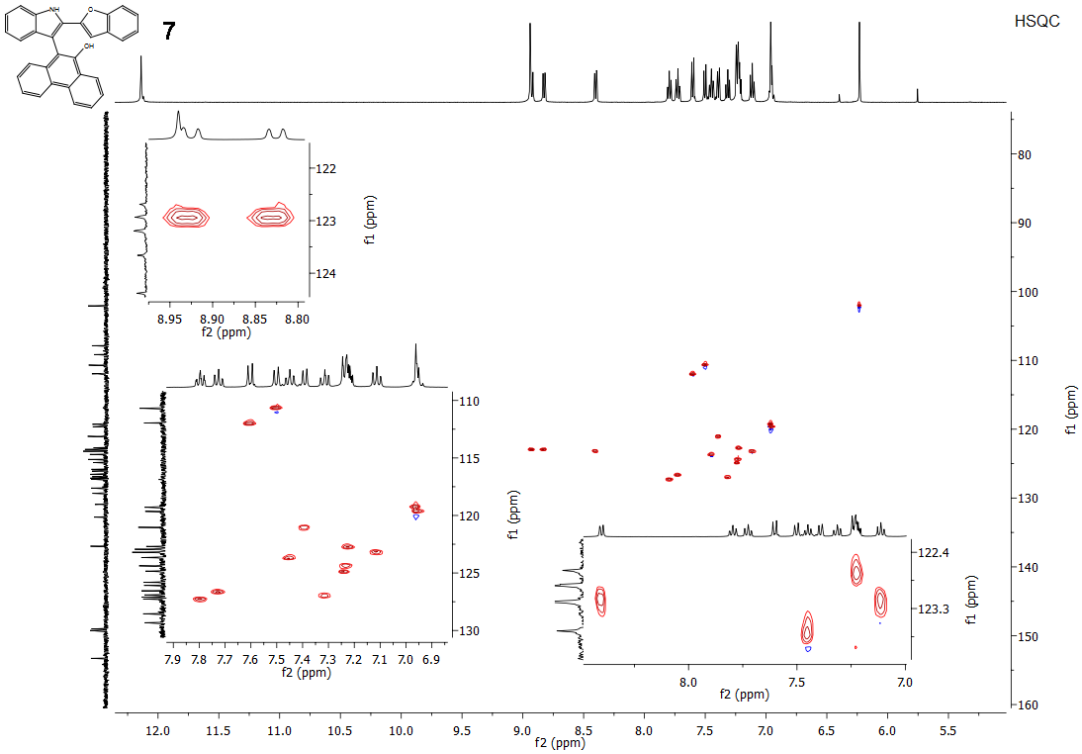

6
HSQC
f2 (ppm)
f1 (ppm)

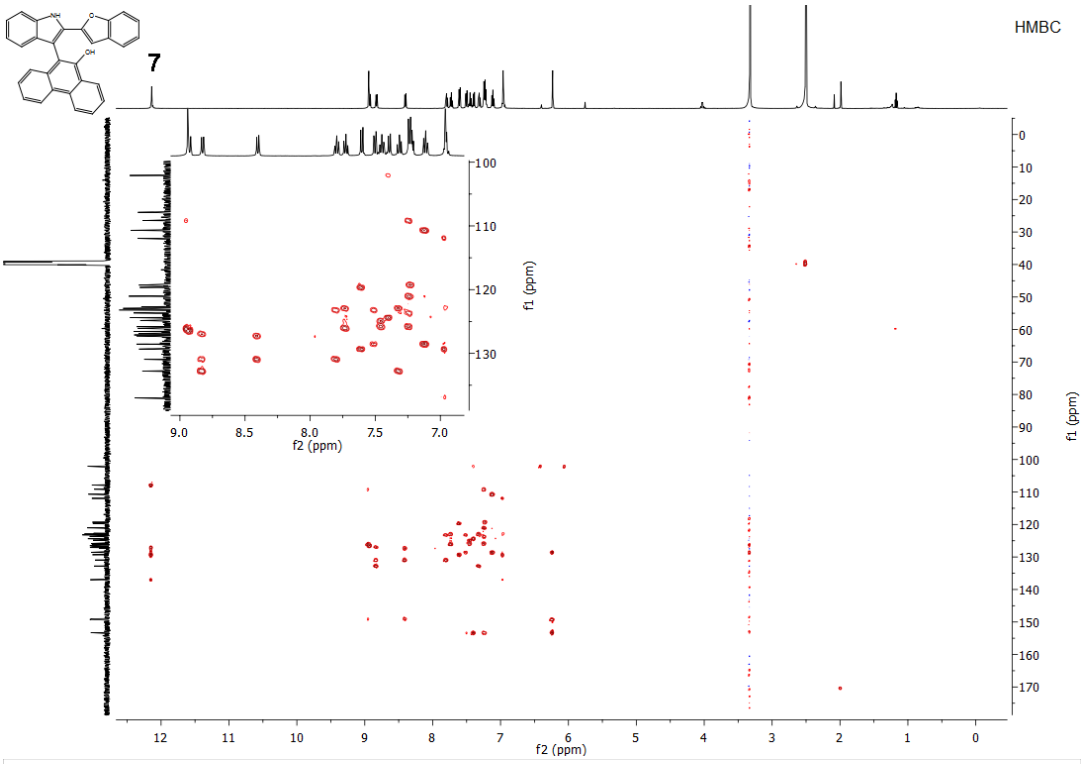

6
HMBC
f2 (ppm)
f1 (ppm)

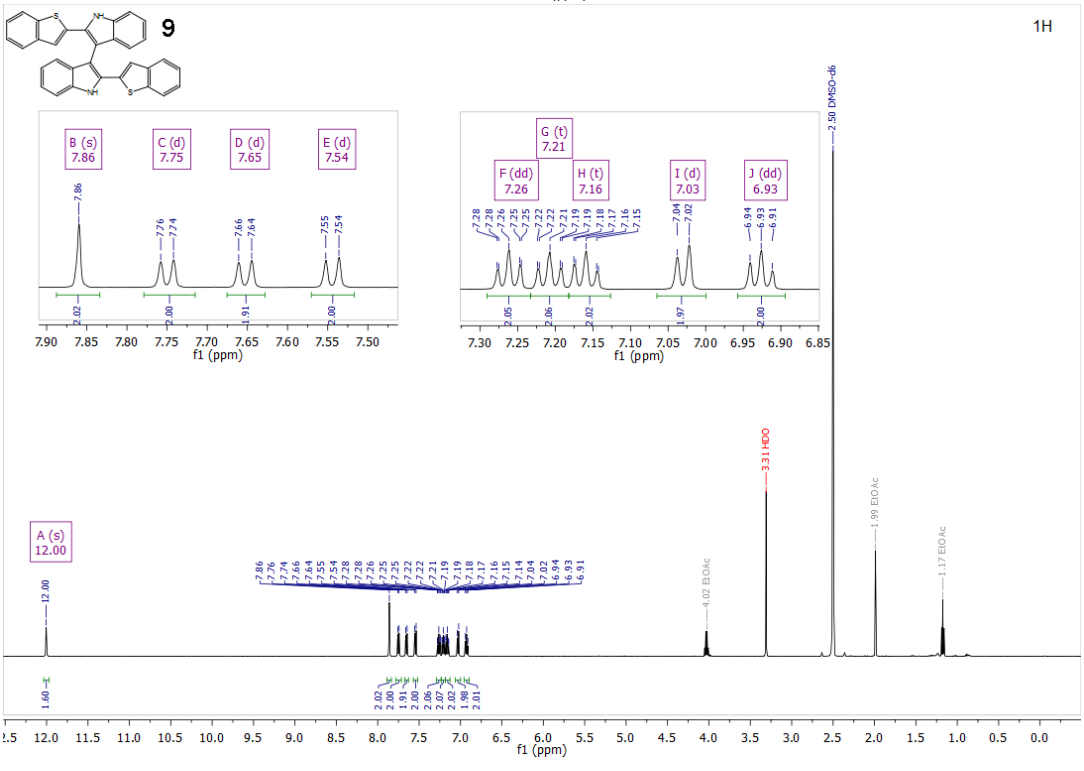

7
1H
A (s) 12.14
B (s) 8.94
C (d) 8.93
D (d) 8.83
E (d) 8.40
F (dd) 7.80
G (dd) 7.73
H (d) 7.60
I (d) 7.50
J (dd) 7.45
K (d) 7.39
L (dd) 7.31
M (m) 7.23
N (dd) 7.11
O (m) 6.96
P (s) 6.23
5.75 CH2Cl2
f1 (ppm)

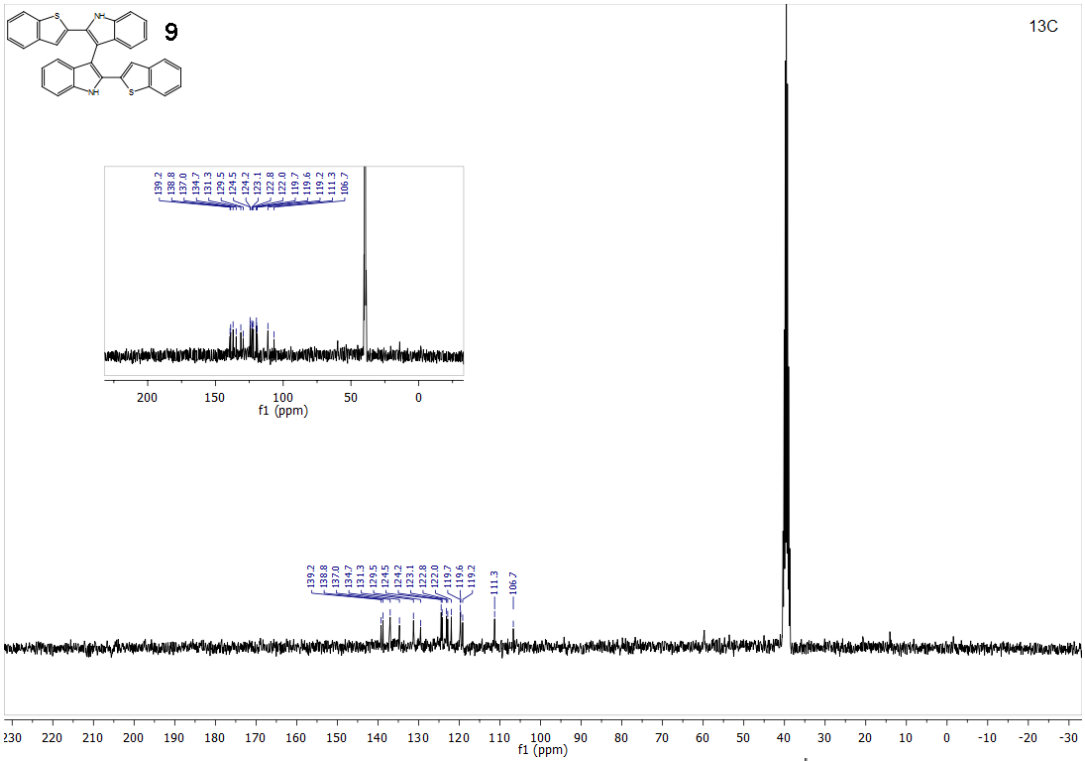

7
13C
175.93
156.58
156.54
155.19
154.18
153.10
137.60
136.79
127.38
125.37
124.31
123.74
121.30
121.22
121.12
112.03
110.86
102.25
63.71
30.94 n-Hex
22.05 n-Hex
14.08 n-Hex
f1 (ppm)

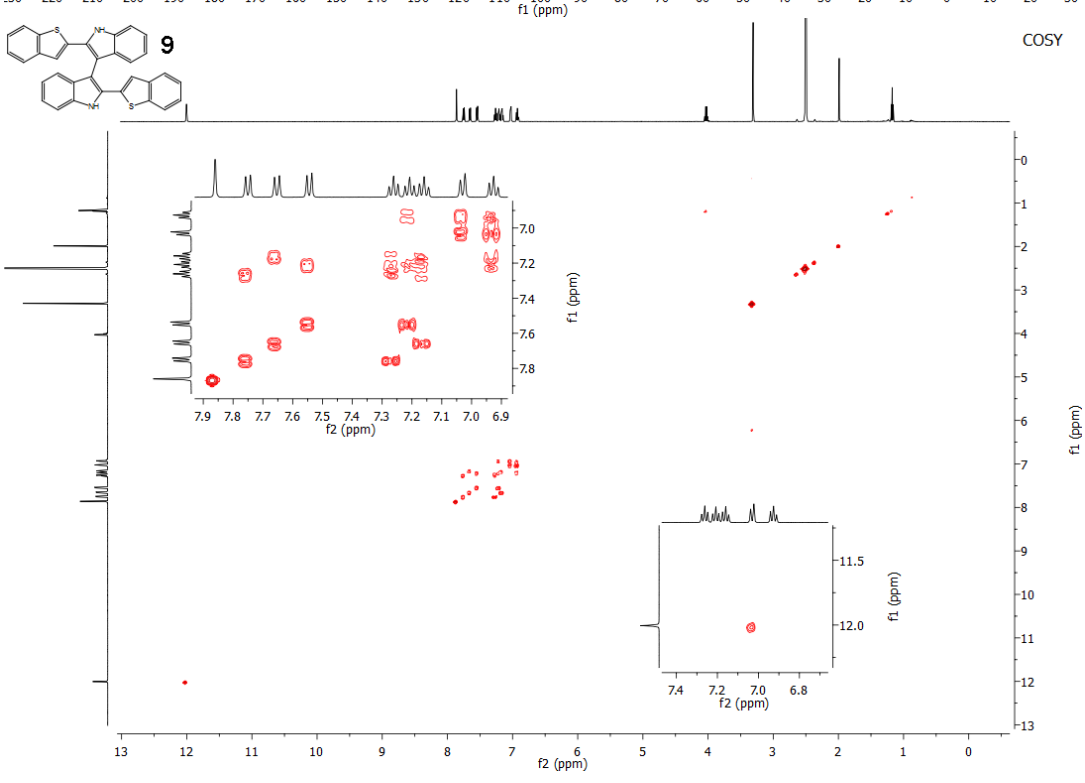

7
COSY
f2 (ppm)
f1 (ppm)

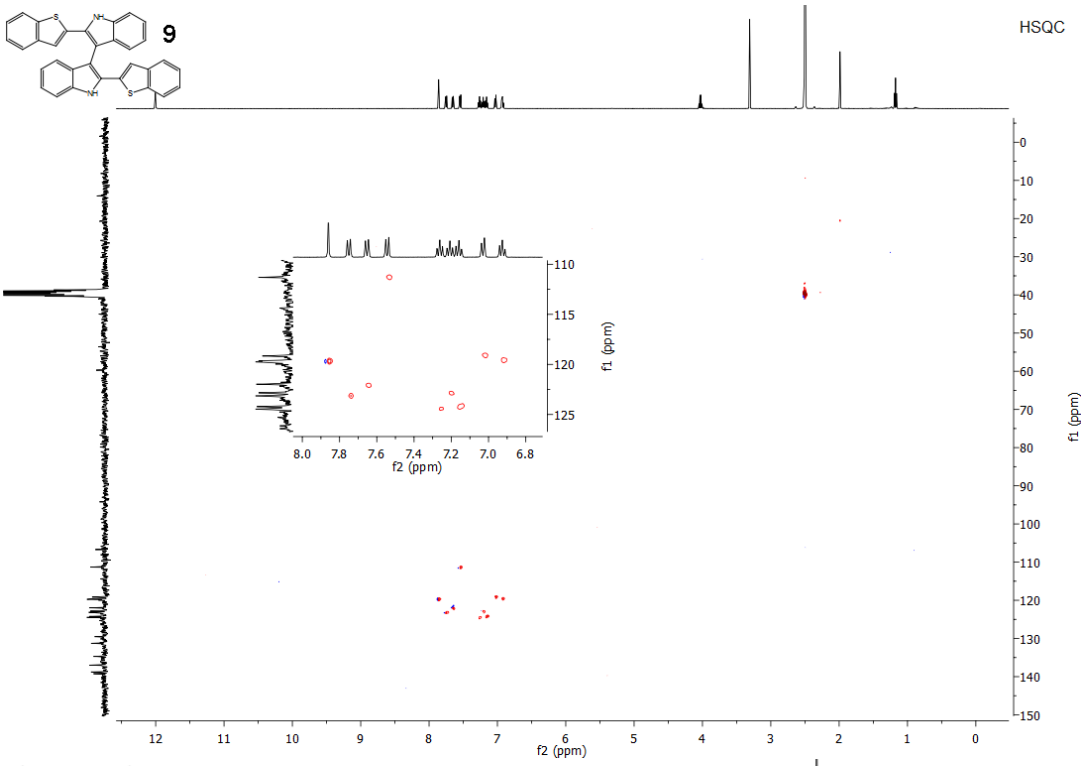

7
HSQC
f2 (ppm)
f1 (ppm)

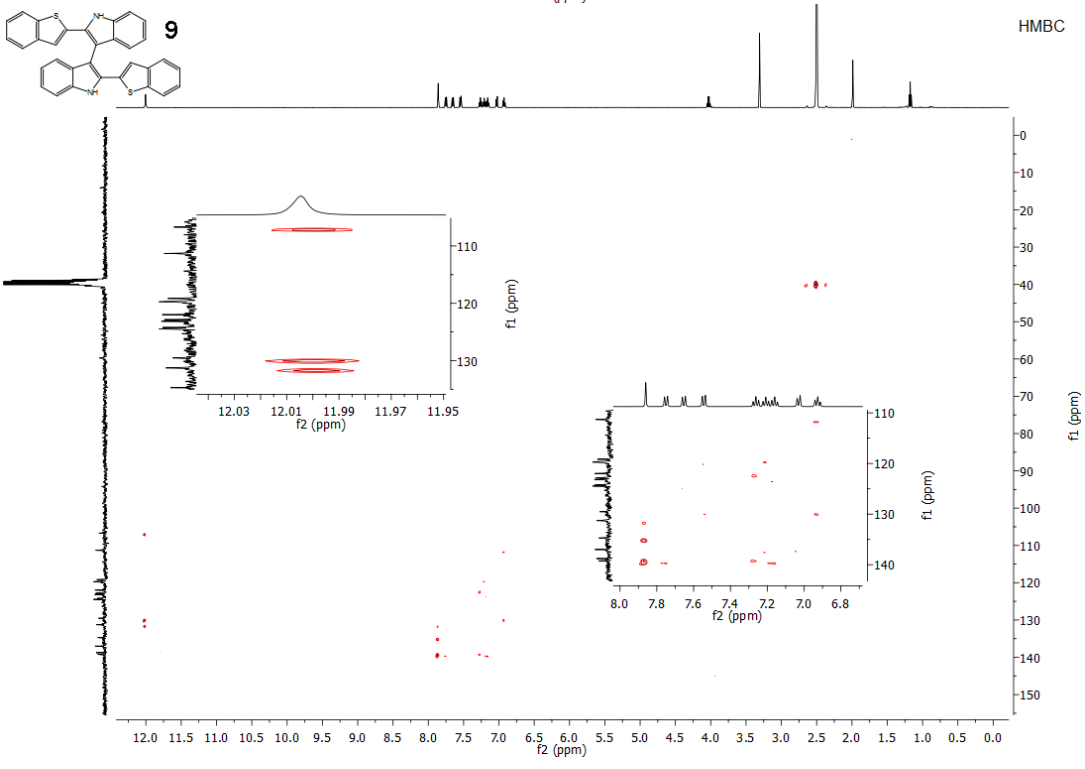

7
HMBC
f2 (ppm)
f1 (ppm)

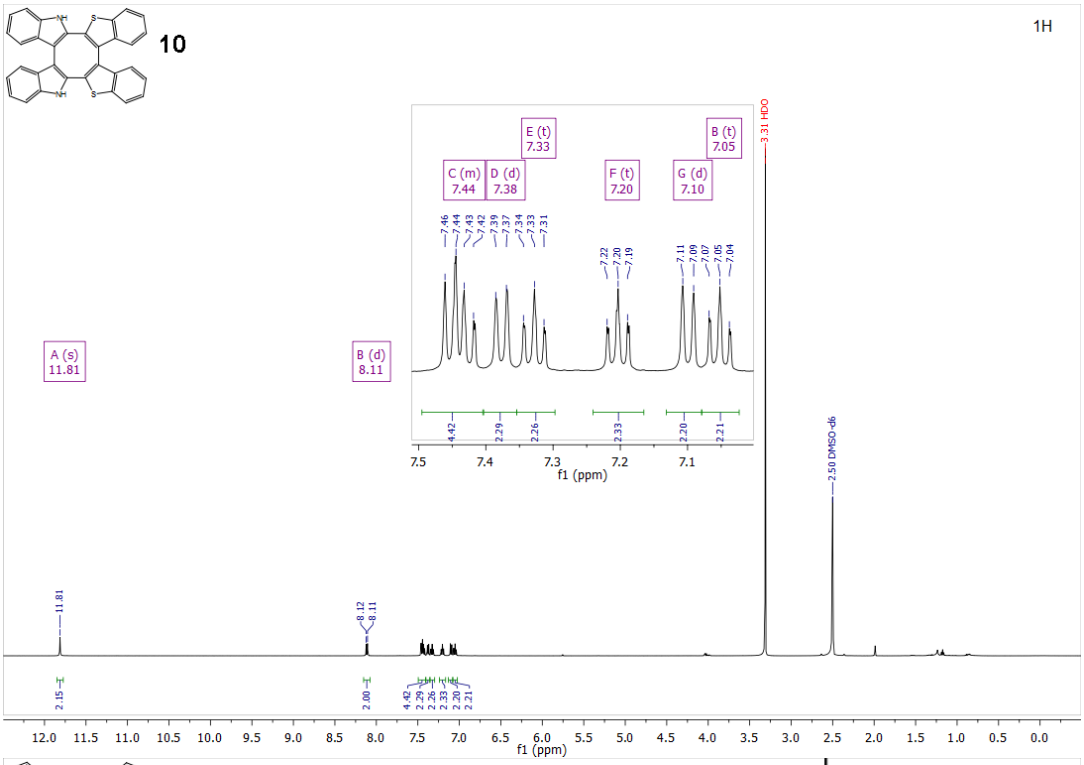

9
1H
B (s) 7.86
C (d) 7.75
D (d) 7.65
E (d) 7.54
F (dd) 7.26
G (t) 7.21
H (t) 7.16
I (d) 7.03
J (dd) 6.93
A (s) 12.00
2.50 DMSO-d6
3.31 HDO
1.99 EtOAc
1.17 EtOAc
4.02 EtOAc
f1 (ppm)

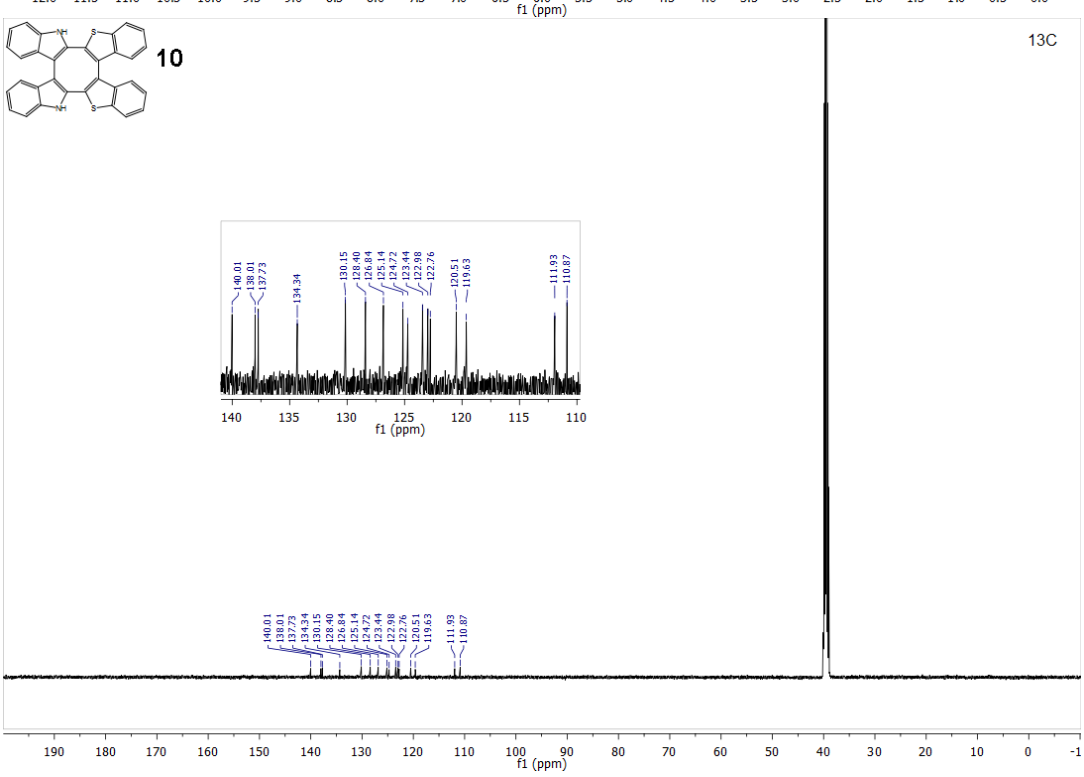

9
13C
139.2
138.8
137.0
134.7
131.3
129.5
124.5
124.2
123.1
122.8
122.0
119.7
119.6
119.2
111.3
106.7
f1 (ppm)

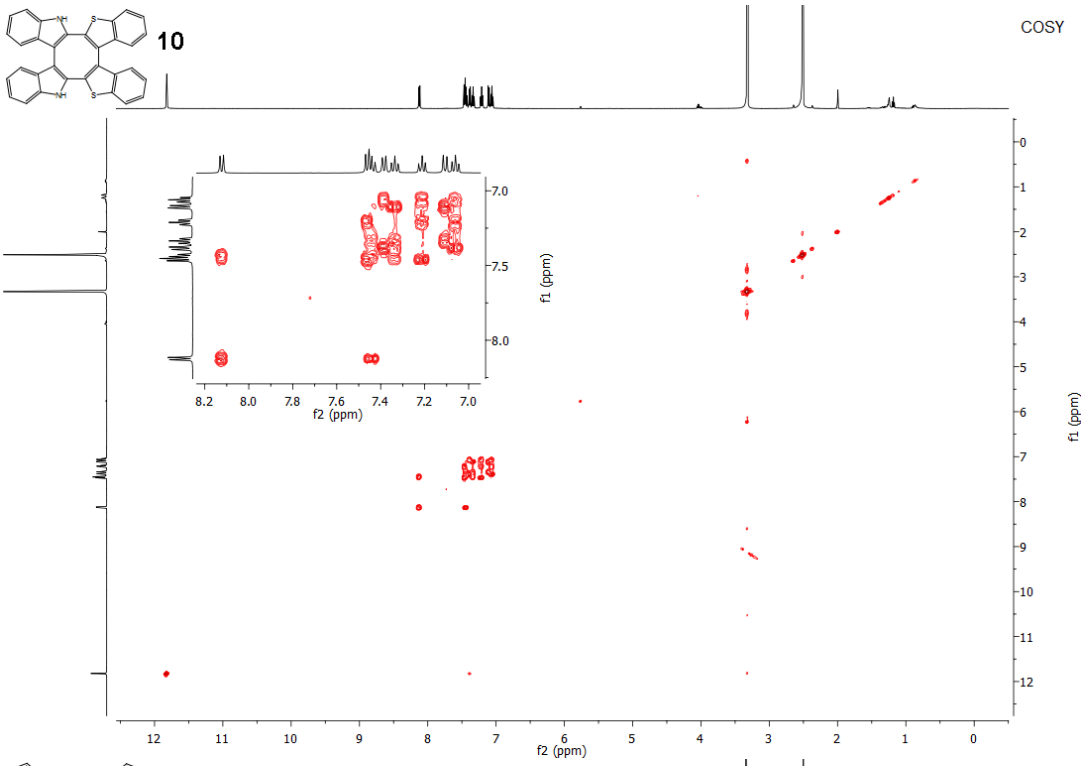

9
COSY
f1 (ppm)
f2 (ppm)

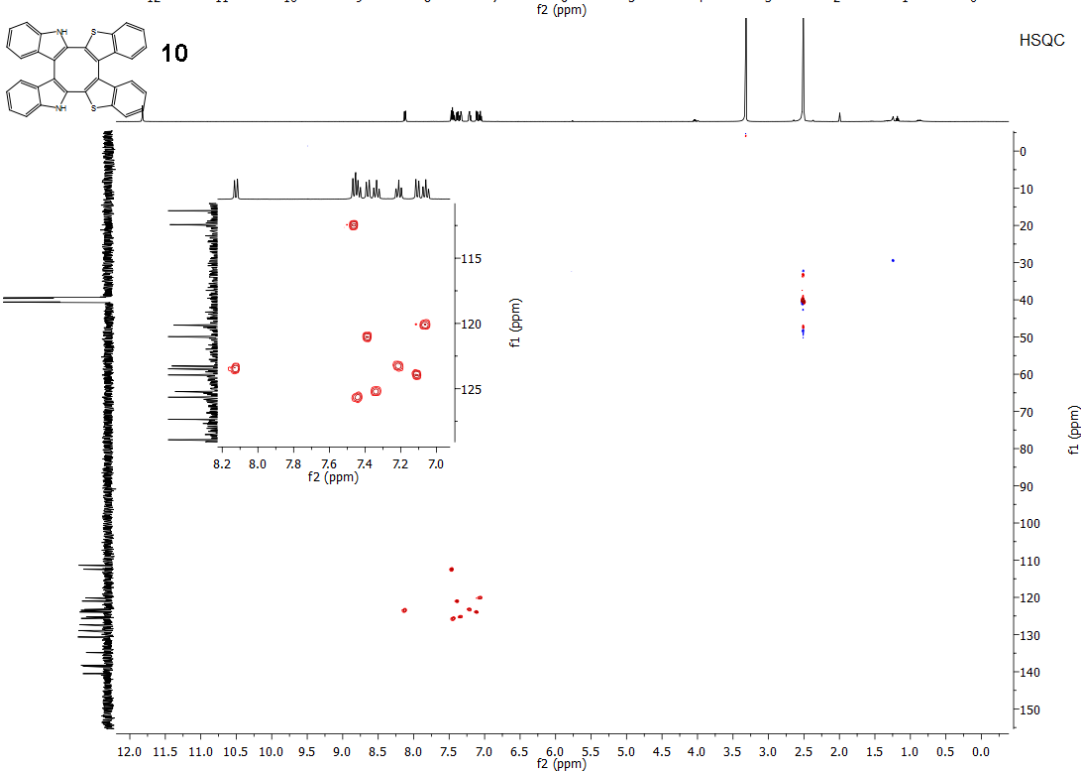

9
HSQC
f2 (ppm)
f1 (ppm)

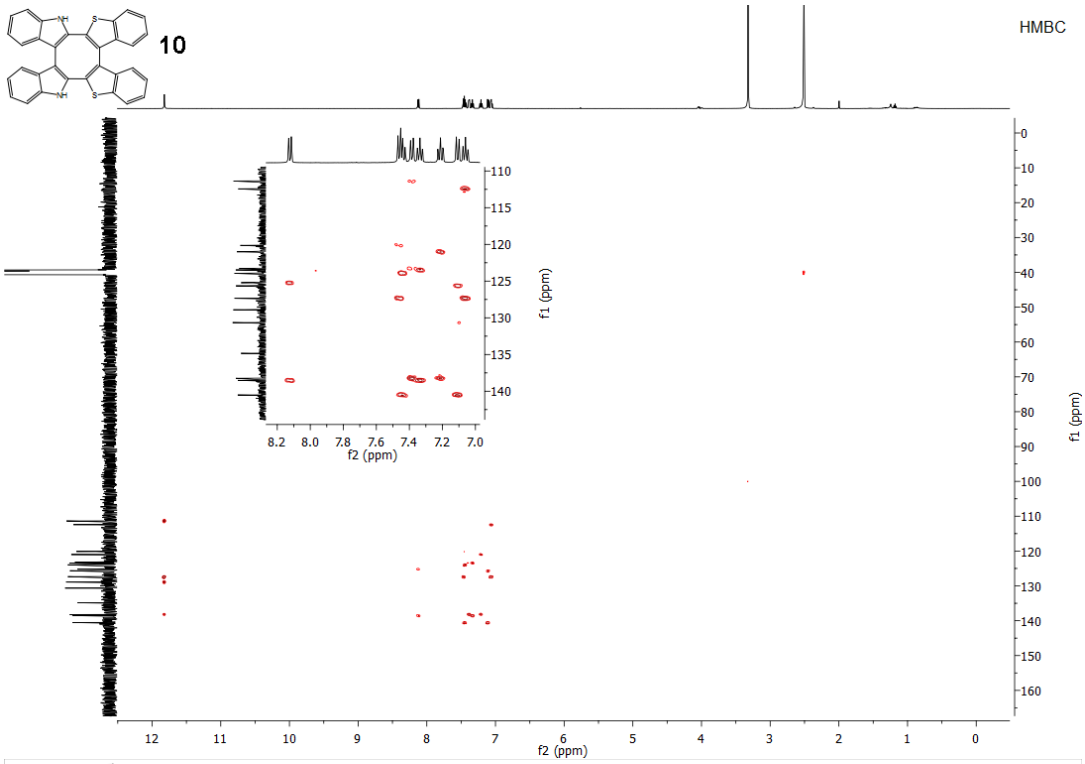

9
HMBC
f2 (ppm)
f1 (ppm)

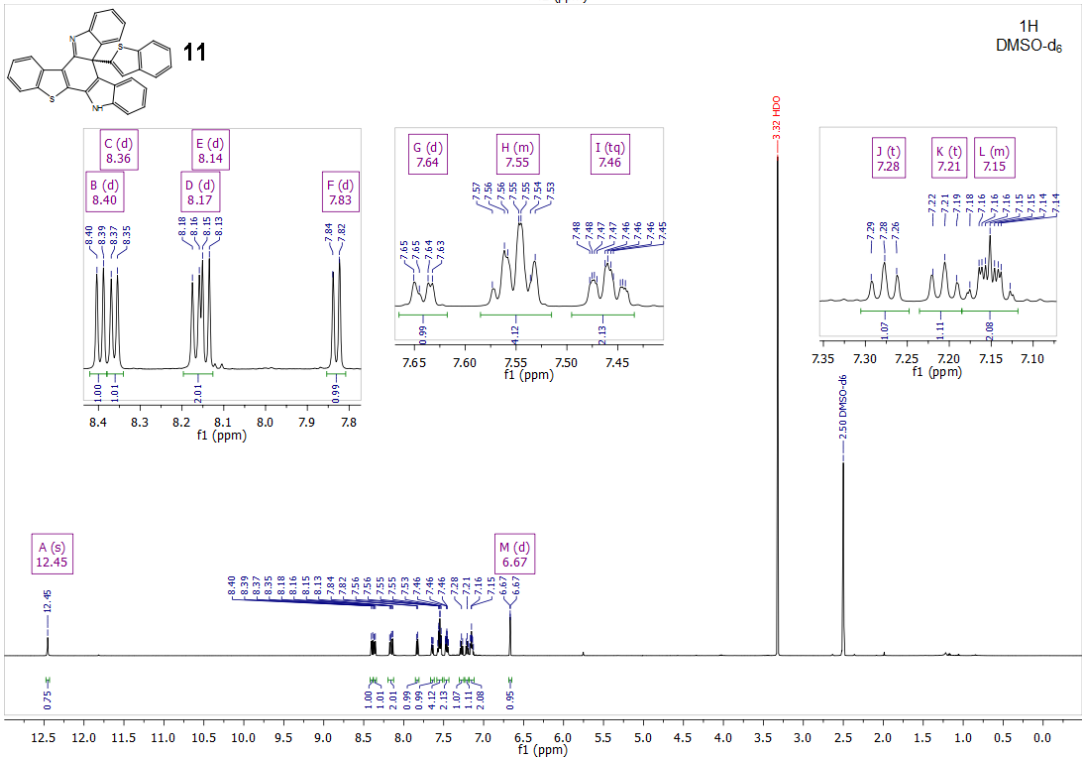

10
1H
A (s)
11.81
B (d)
8.11
E (t)
7.33
C (m)
7.44
D (d)
7.38
F (t)
7.20
G (d)
7.10
B (t)
7.05
3.31 HDO
2.50 DMSO-d6
f1 (ppm)

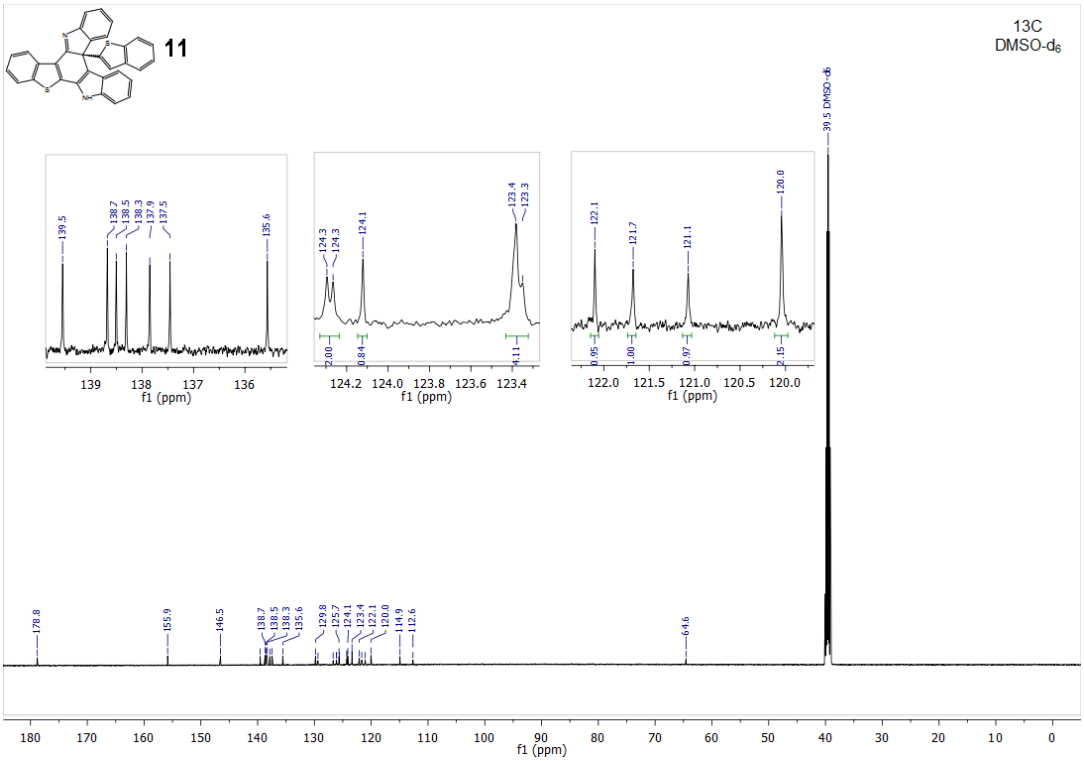

10
13C
f1 (ppm)

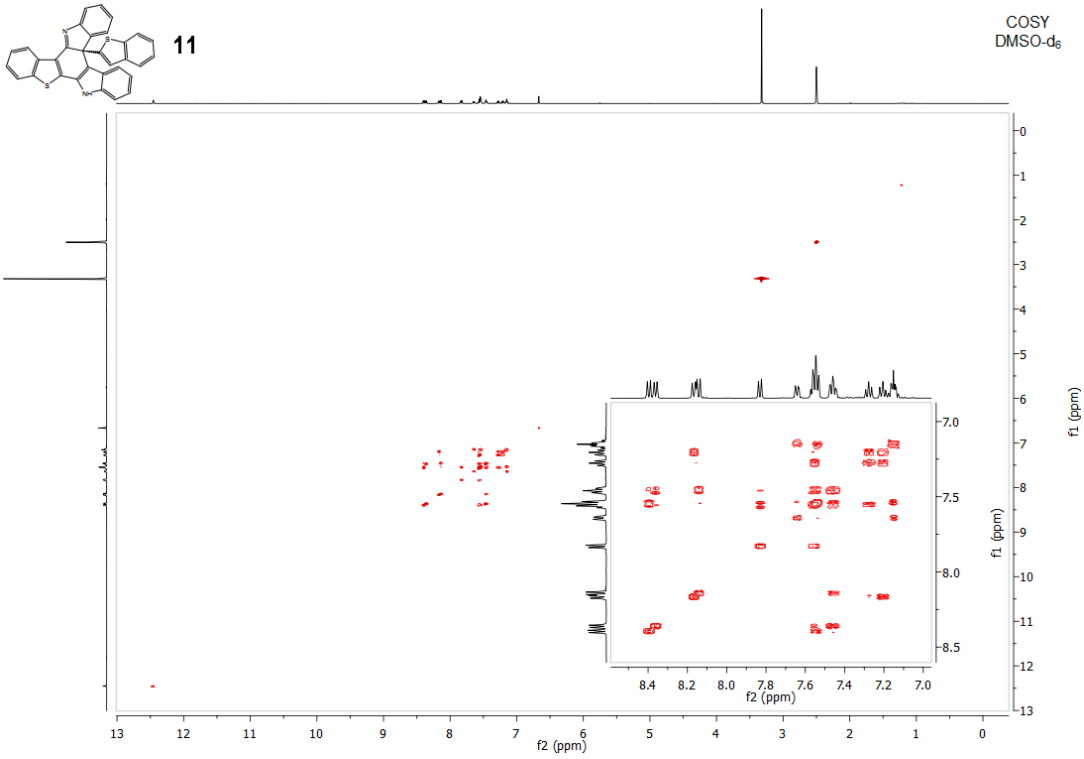

10
COSY
f1 (ppm)
f2 (ppm)

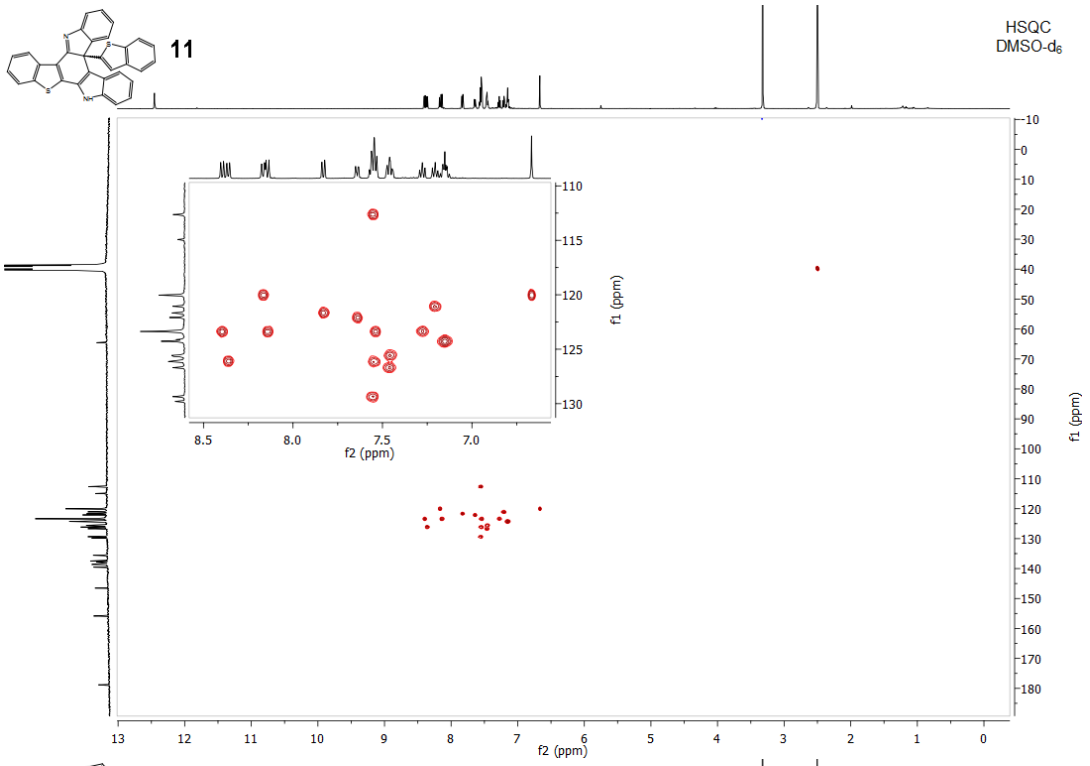

10
HSQC
f1 (ppm)
f2 (ppm)

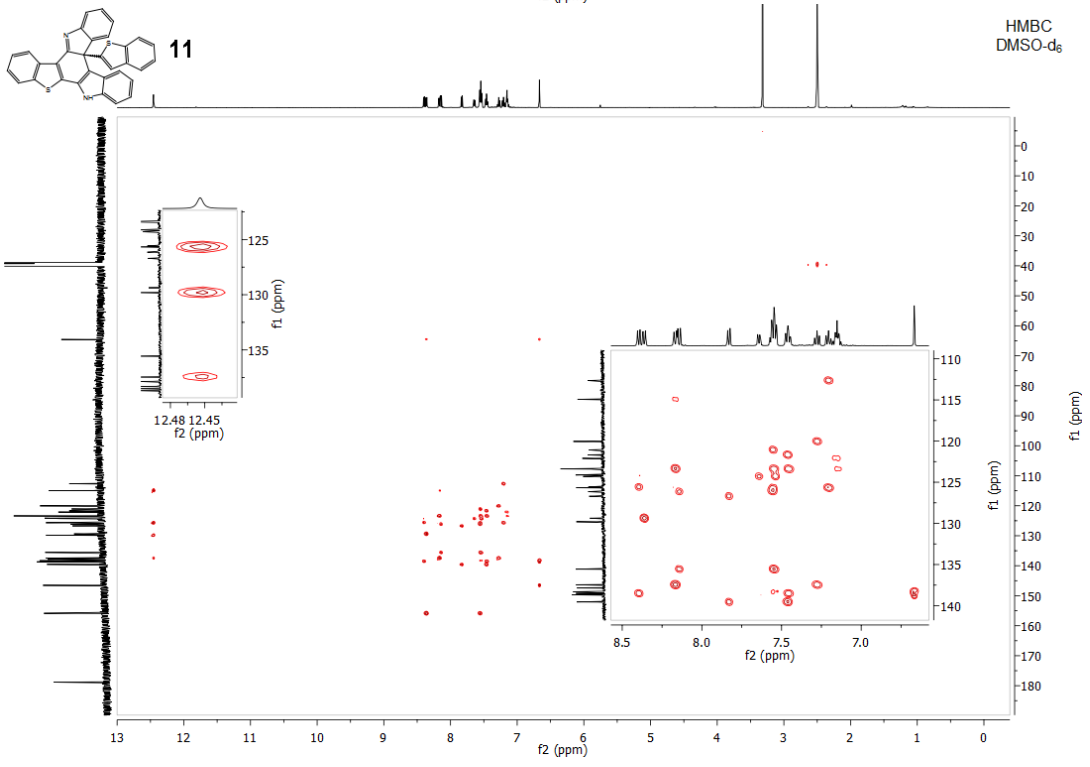

10
HMBC
f1 (ppm)
f2 (ppm)

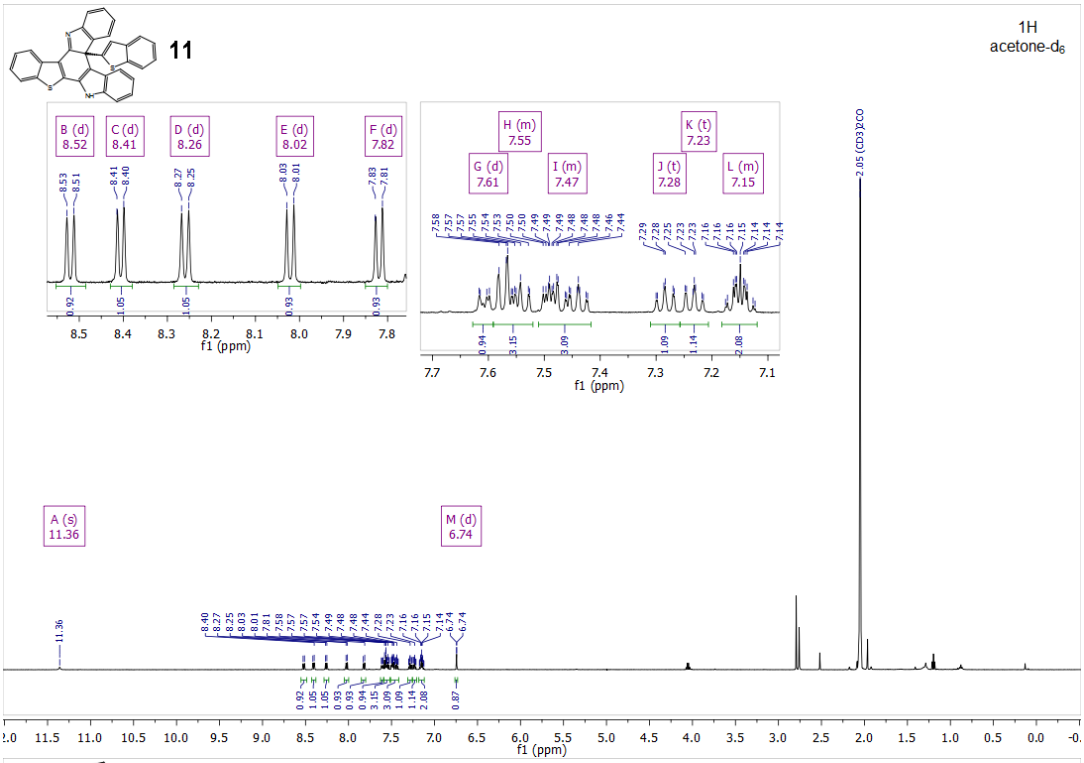

11
1H
DMSO-d6
A (s) 12.45
B (d) 8.40
C (d) 8.36
D (d) 8.17
E (d) 8.14
F (d) 7.83
G (d) 7.64
H (m) 7.55
I (tq) 7.46
J (t) 7.28
K (t) 7.21
L (m) 7.15
M (d) 6.67
3.32 HDO
2.50 DMSO-d6
f1 (ppm)

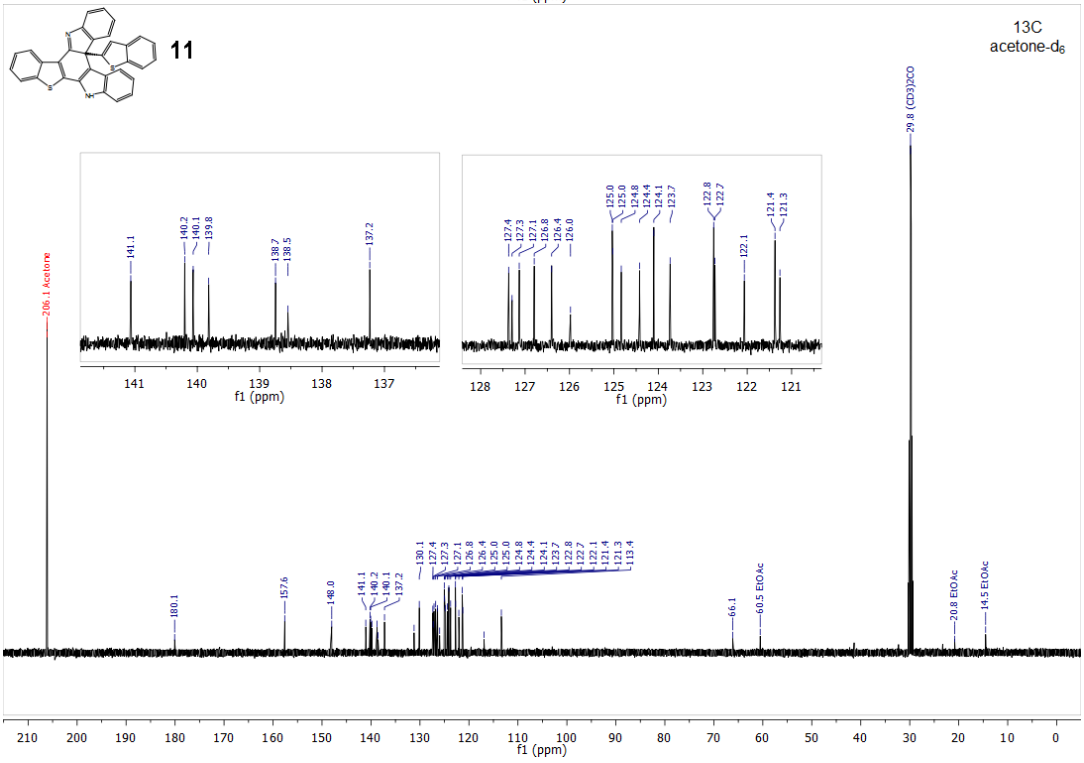

11
13C
DMSO-d6
39.5 DMSO-d6
139.5
138.7
138.5
138.3
137.9
137.5
135.6
124.3
124.3
124.1
123.4
123.3
122.1
121.7
121.1
120.0
178.8
155.9
146.5
138.7
138.5
138.3
135.6
129.8
125.7
124.1
123.4
122.1
120.0
114.9
112.6
64.6
f1 (ppm)

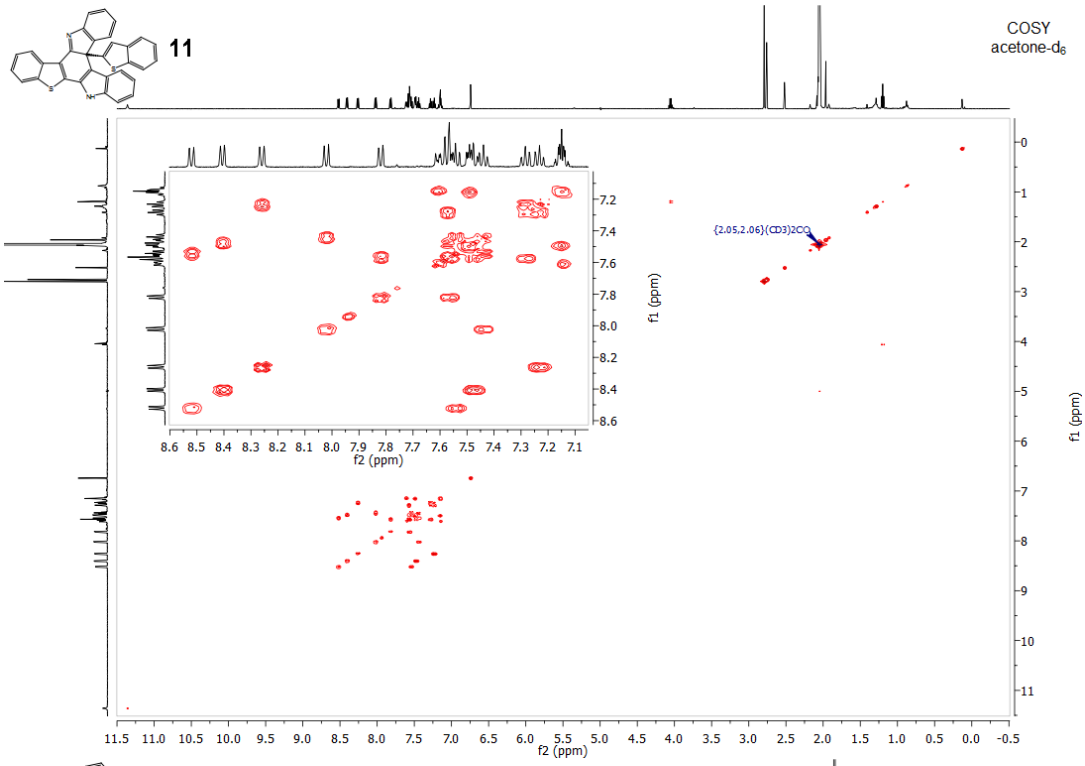

11
COSY
DMSO-d6
f1 (ppm)
f2 (ppm)

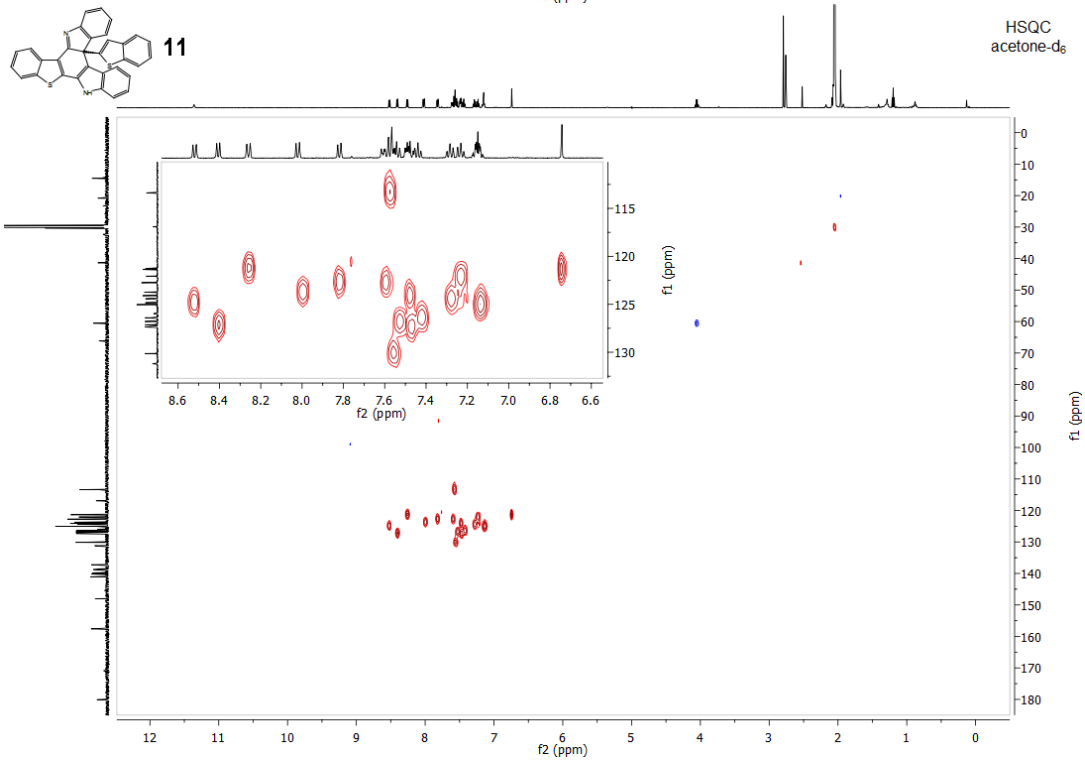

11
HSQC
DMSO-d6
f2 (ppm)
f1 (ppm)

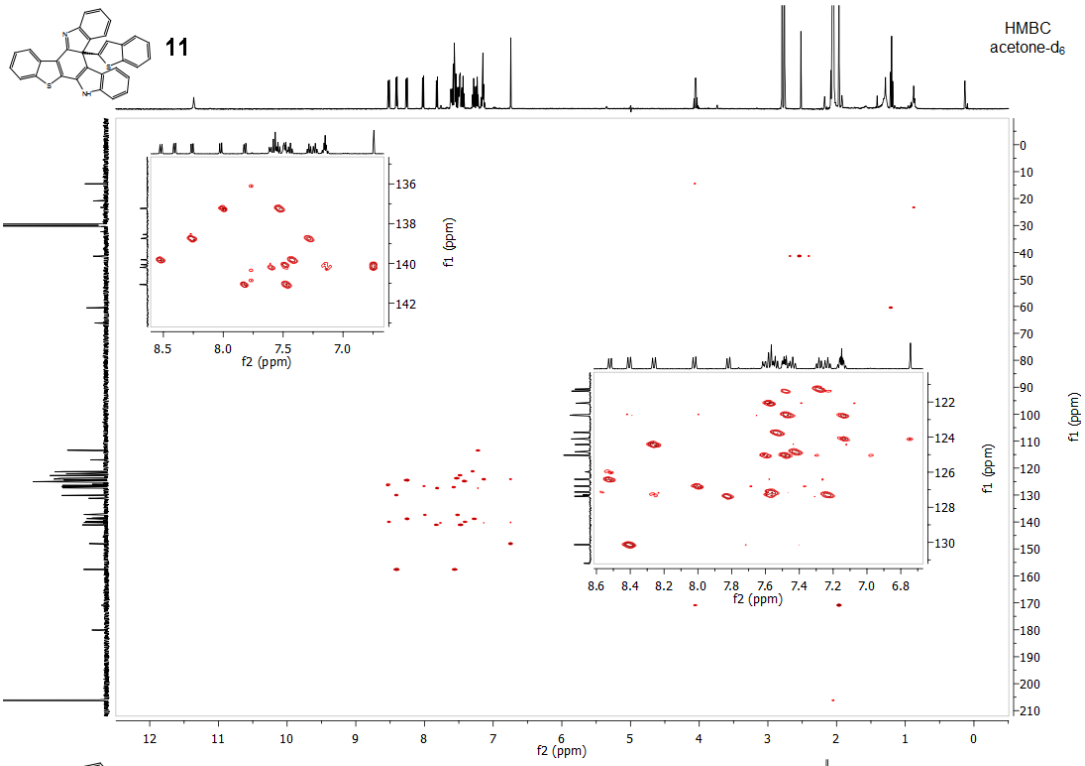

11
HMBC
DMSO-d6
f2 (ppm)
f1 (ppm)

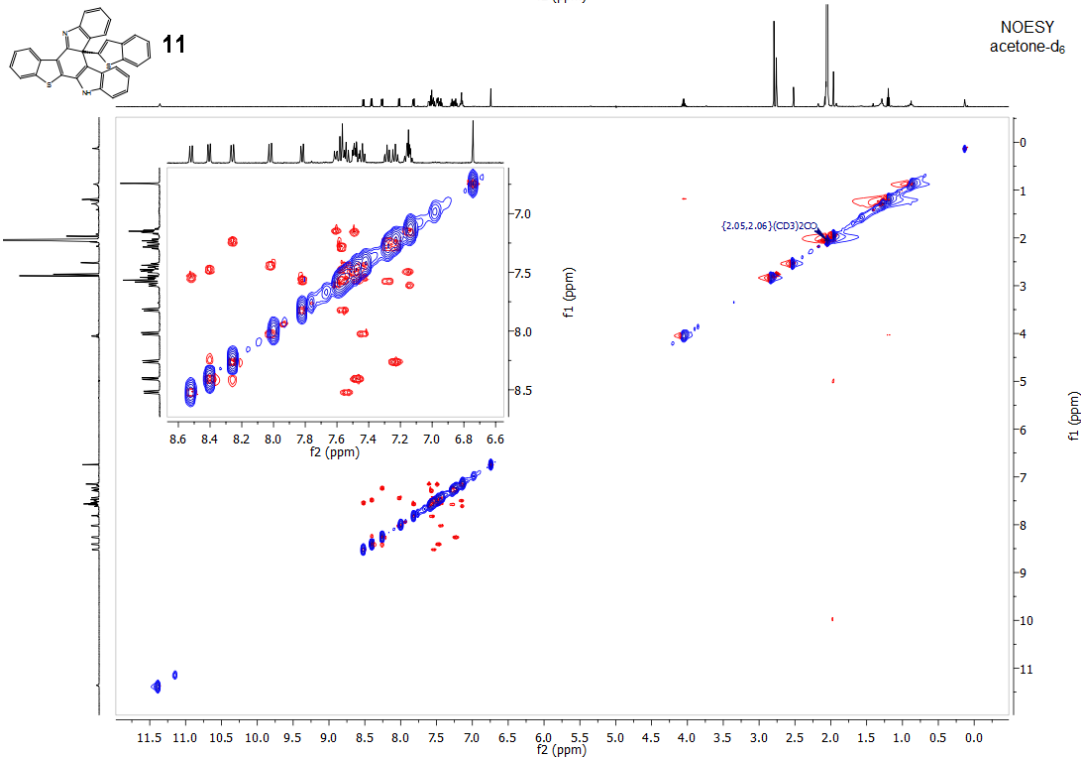

11
1H
acetone-d6
B (d) 8.52
C (d) 8.41
D (d) 8.26
E (d) 8.02
F (d) 7.82
G (d) 7.61
H (m) 7.55
I (m) 7.47
J (t) 7.28
K (t) 7.23
L (m) 7.15
A (s) 11.36
M (d) 6.74
2.05 (CD3)2CO
f1 (ppm)

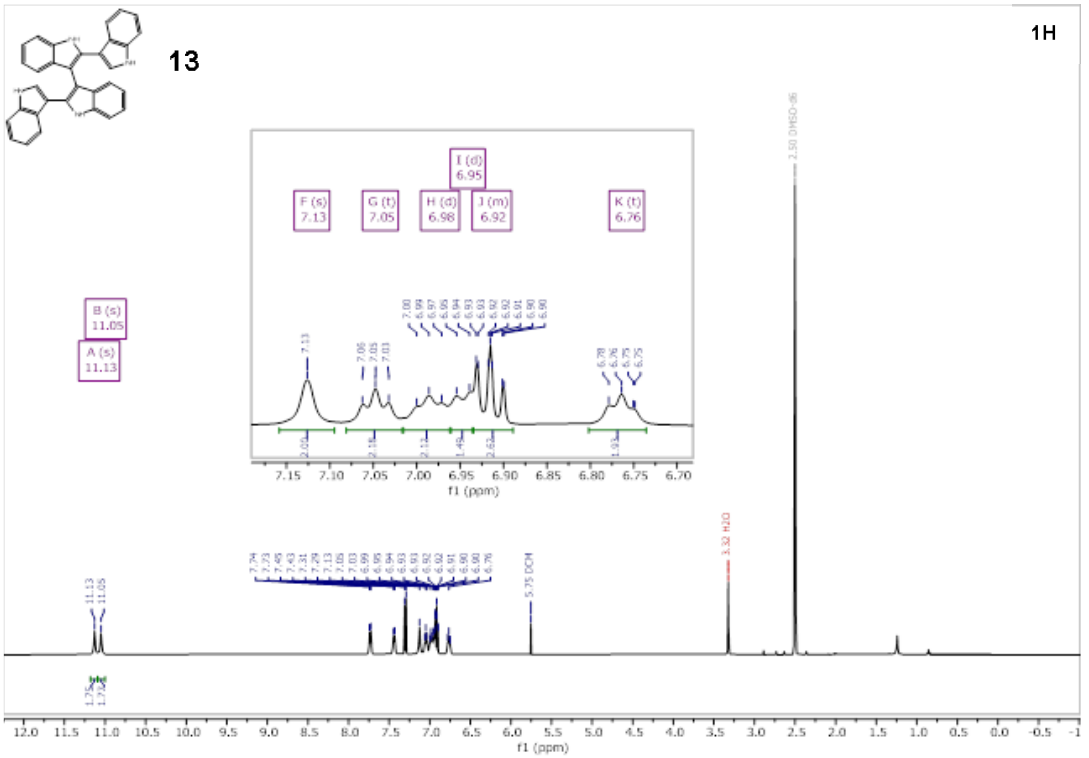

11
13C
acetone-d6
206.1 Acetone
29.8 (CD3)2CO
20.8 EtOAc
14.5 EtOAc
60.5 EtOAc
66.1
f1 (ppm)

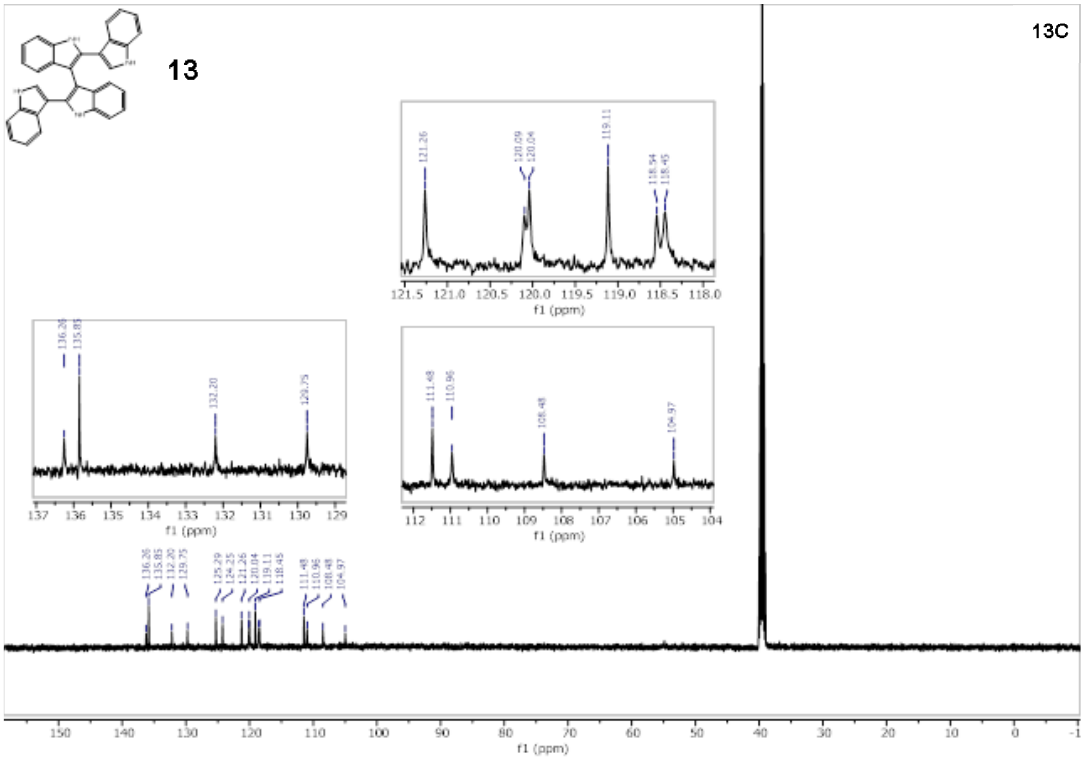

11
COSY
acetone-d6
{2.05,2.06}(CD3)2CO
f1 (ppm)
f2 (ppm)

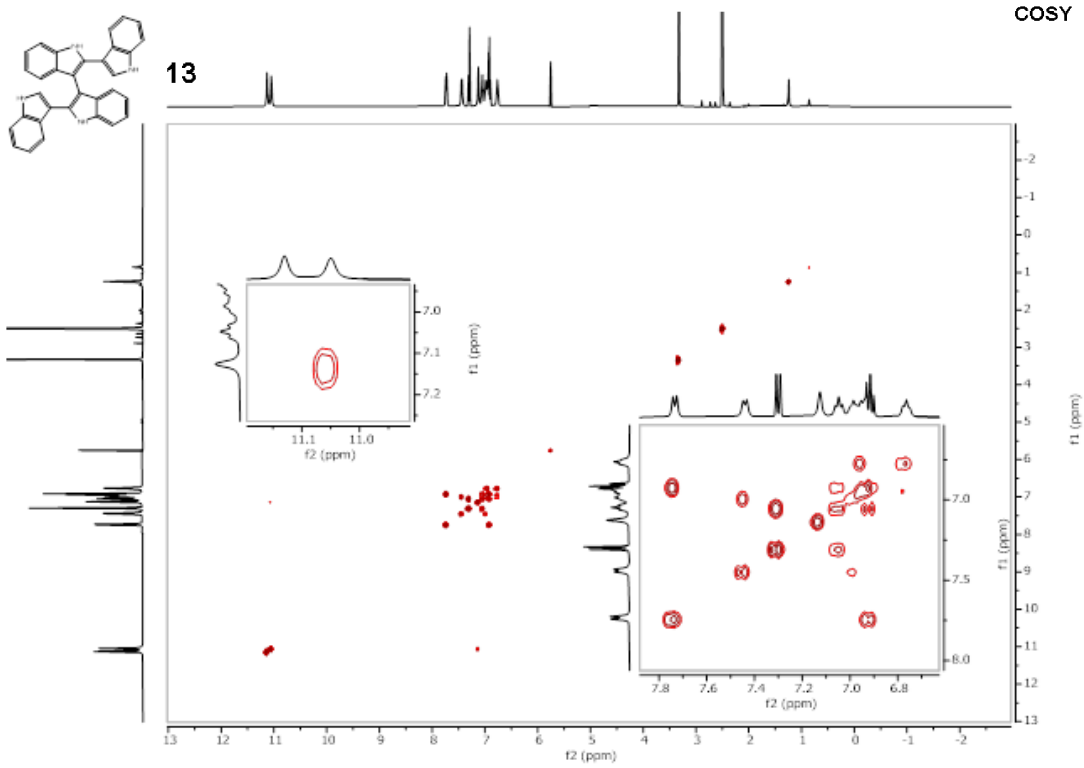

11
HSQC
acetone-d6
f1 (ppm)
f2 (ppm)

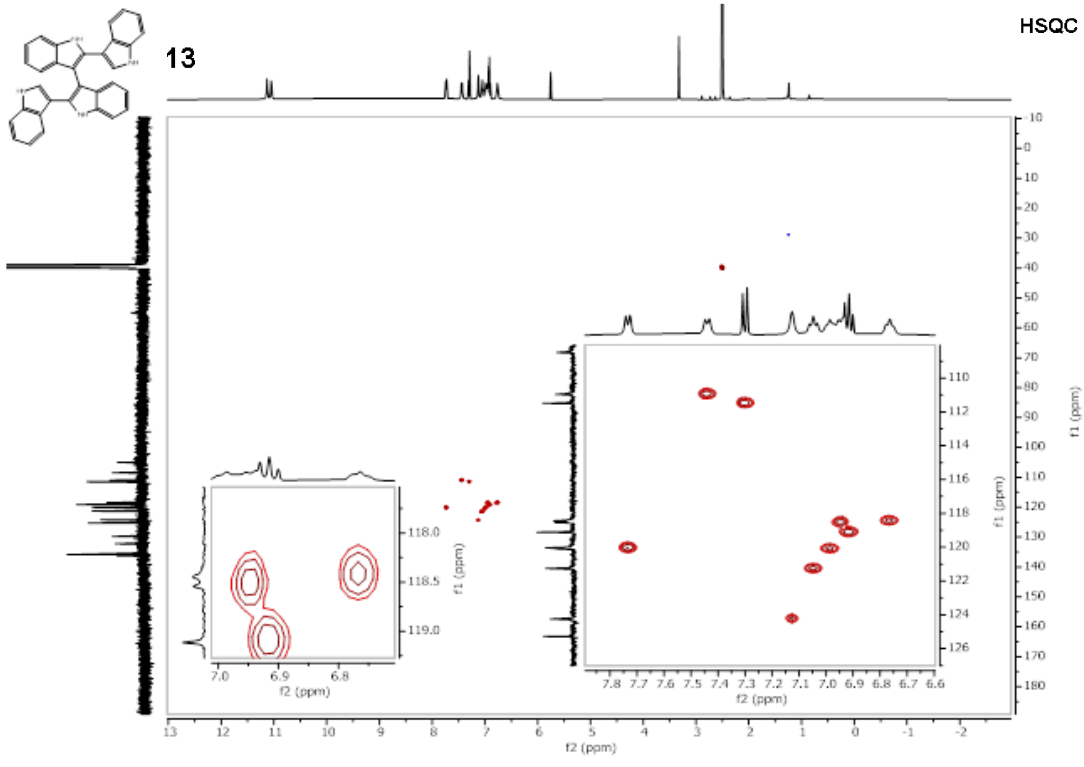

11
HMBC
acetone-d6
f2 (ppm)
f1 (ppm)

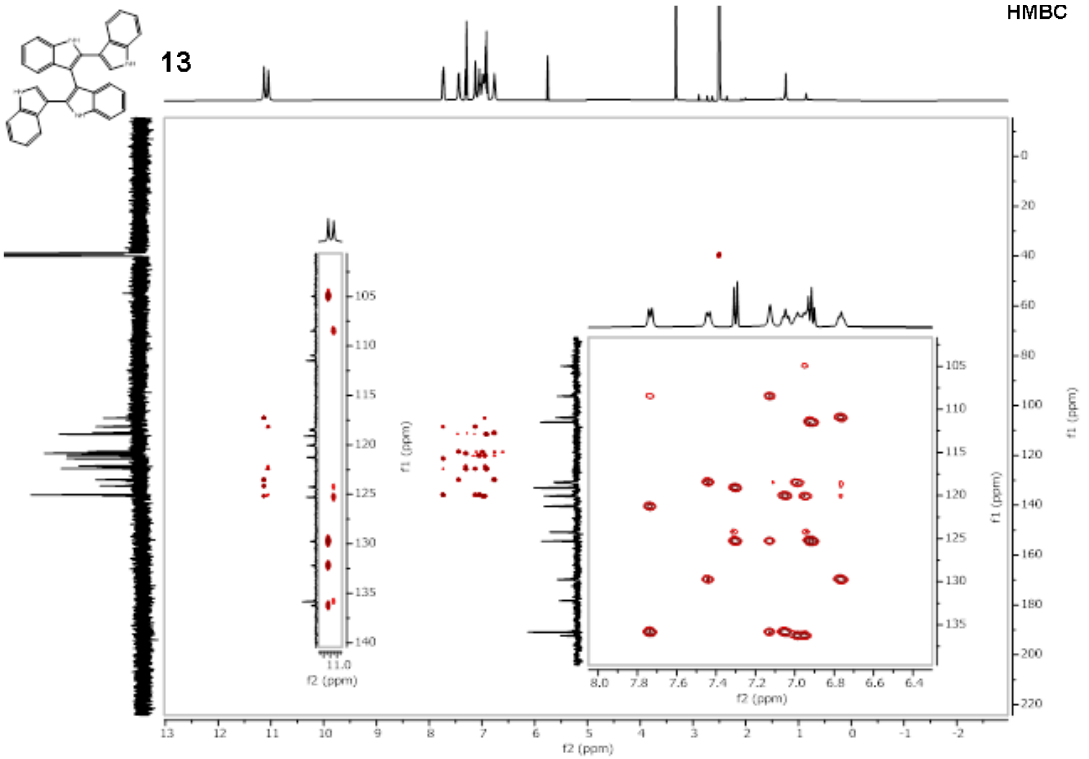

11
NOESY
acetone-d6
{2.05,2.06}(CD3)2CO
f2 (ppm)
f1 (ppm)

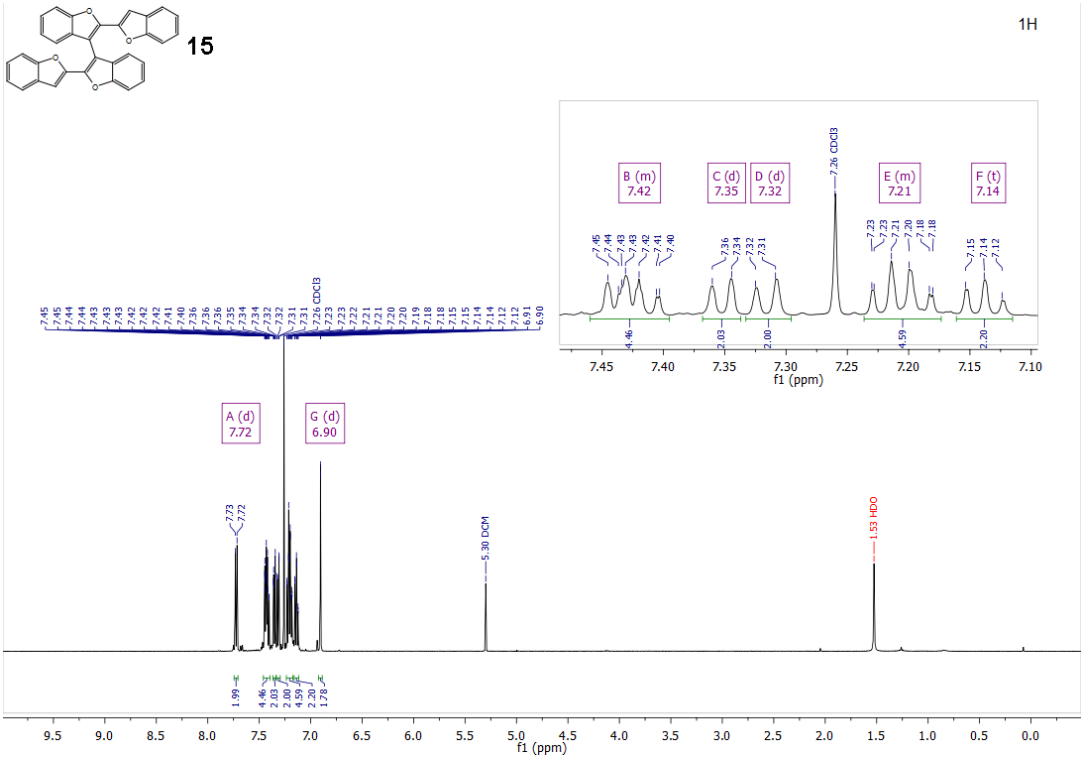

13
1H
F (s) 7.13
G (t) 7.05
H (d) 6.98
I (d) 6.95
J (m) 6.92
K (t) 6.76
B (s) 11.05
A (s) 11.13
2.50 DMSO-d6
3.32 H2O
5.75 DCM
f1 (ppm)

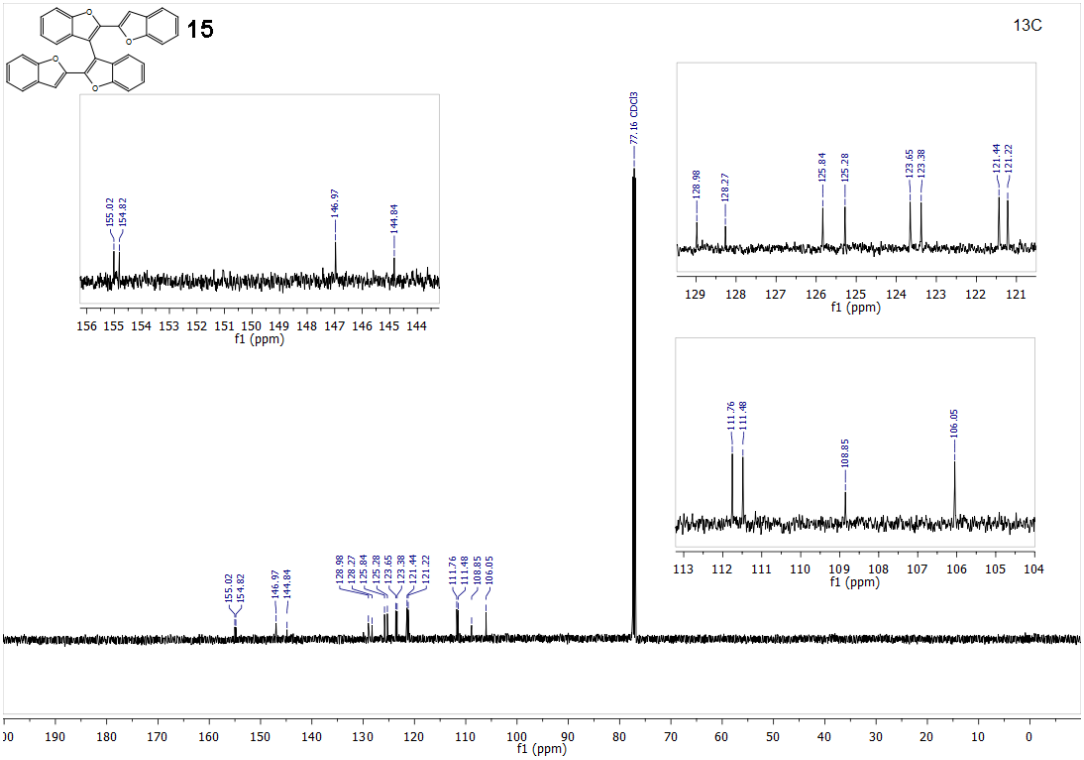

13
13C
121.26
120.09
120.04
119.11
118.94
118.45
136.26
135.85
132.20
129.75
111.48
110.96
108.48
104.97
f1 (ppm)

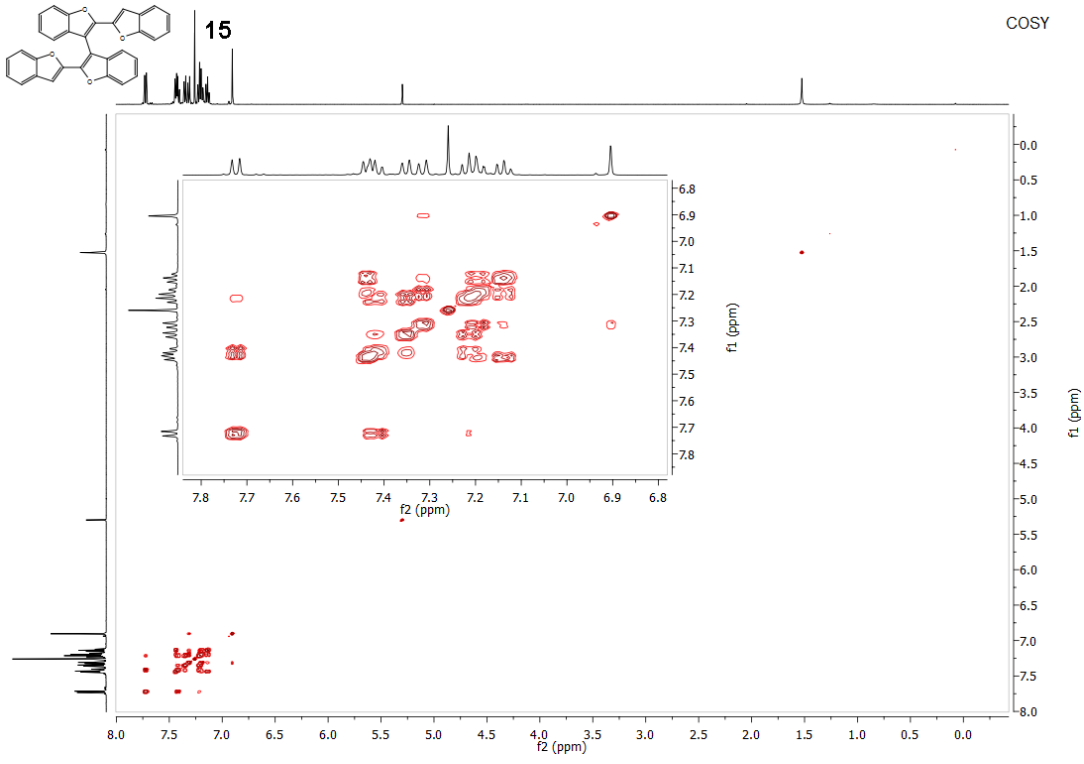

COSY
13
f2 (ppm)
f1 (ppm)

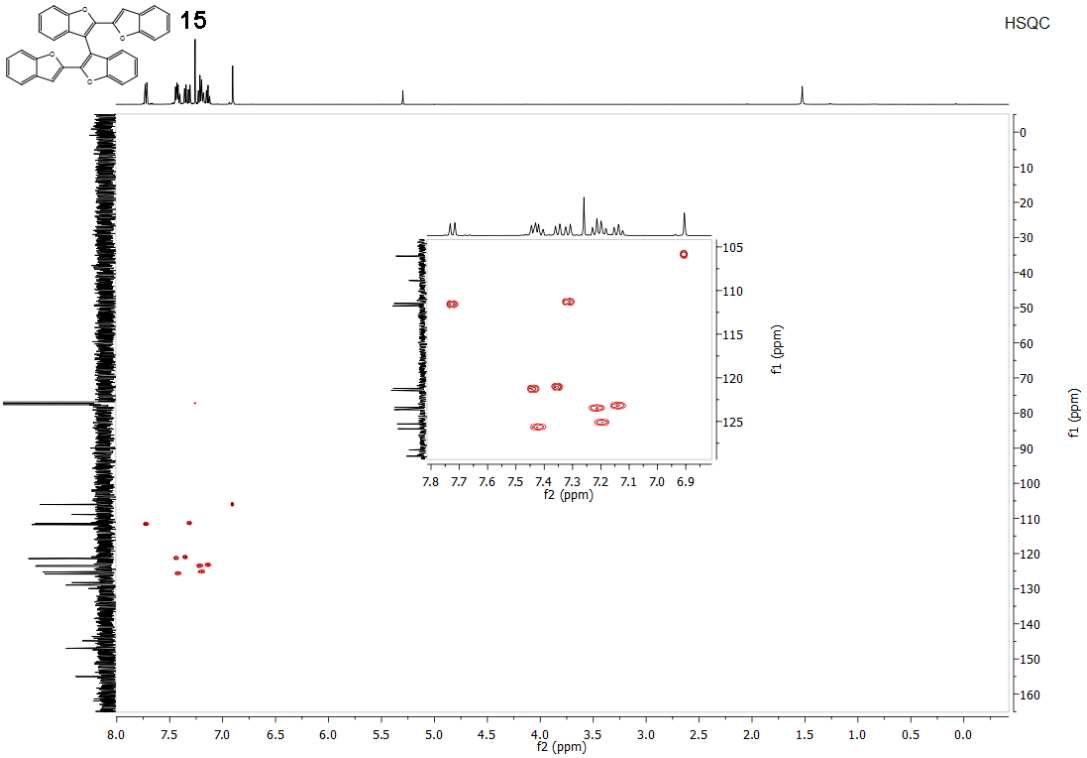

HSQC
13
f2 (ppm)
f1 (ppm)

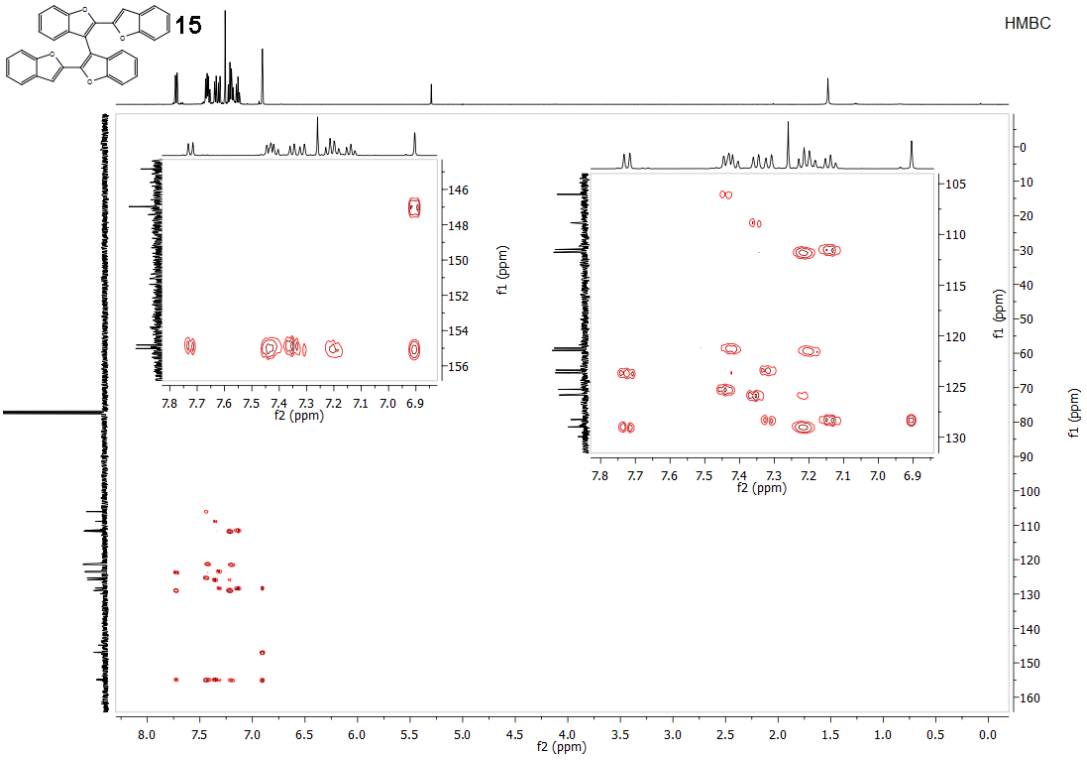

HMBC
13
f2 (ppm)
f1 (ppm)

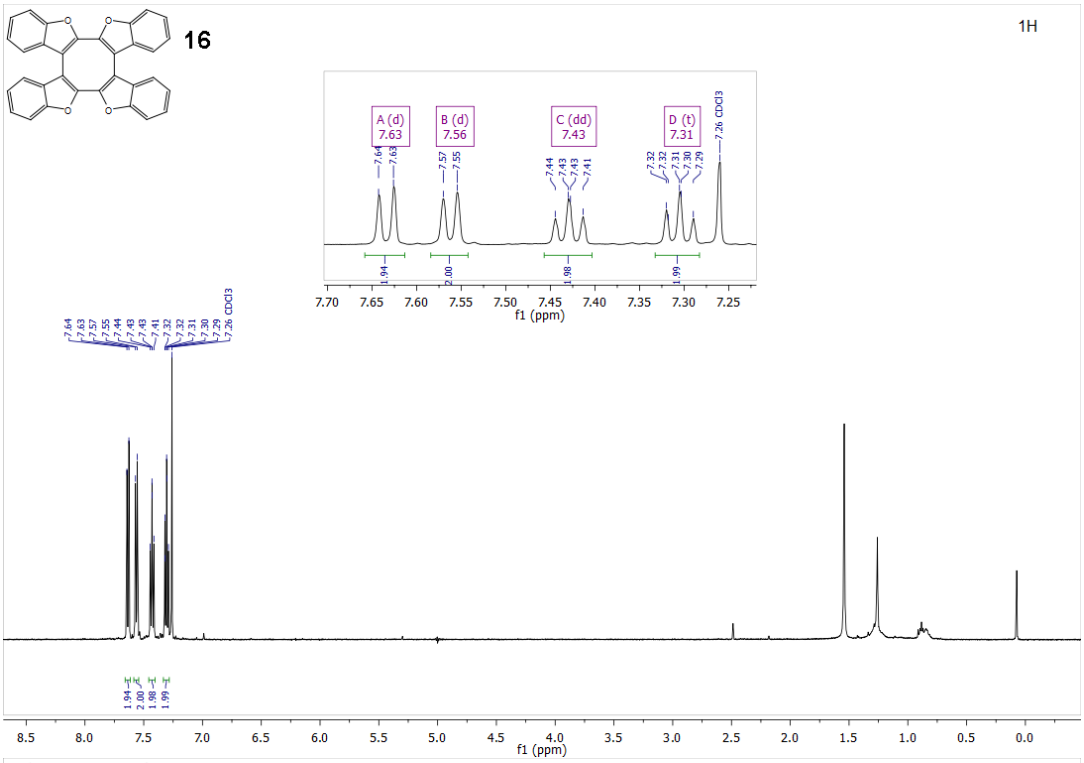

15
1H
B (m) 7.42
C (d) 7.35
D (d) 7.32
E (m) 7.21
F (t) 7.14
A (d) 7.72
G (d) 6.90
7.26 CDCl3
5.30 DCM
1.53 H2O
f1 (ppm)

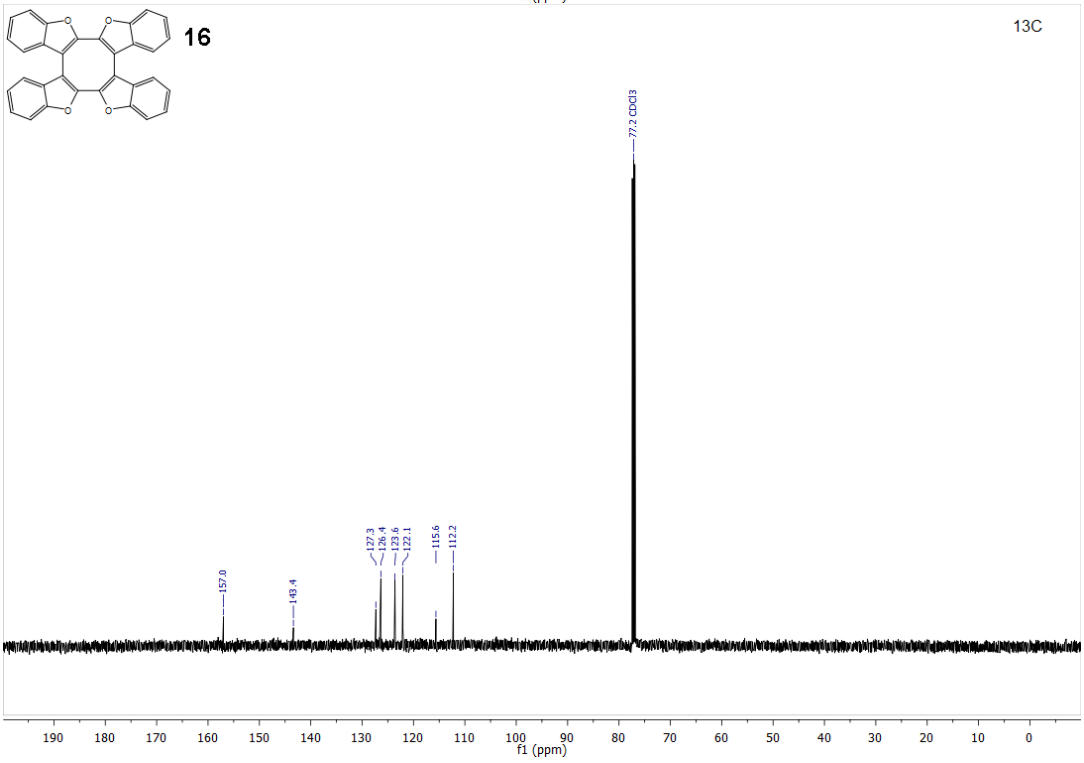

15
13C
77.16 CDCl3
155.02
154.82
146.97
144.84
128.98
128.27
125.84
125.28
123.65
123.38
121.44
121.22
111.76
111.48
108.85
106.05
f1 (ppm)

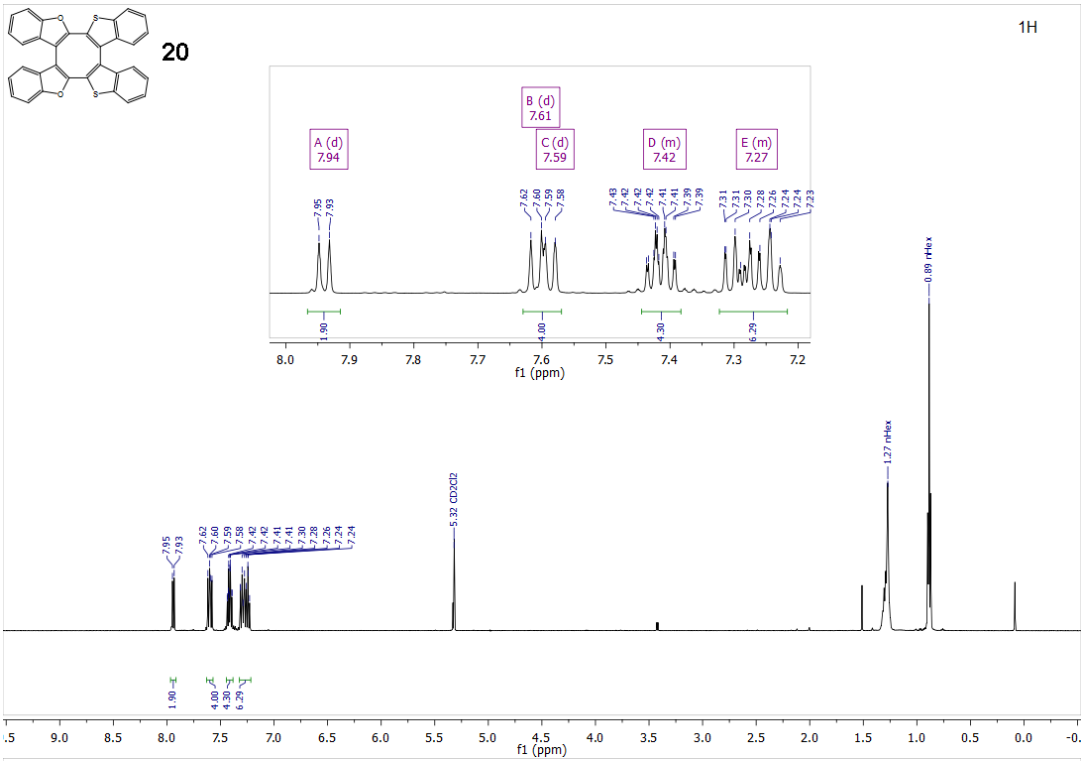

15
COSY
f1 (ppm)
f2 (ppm)

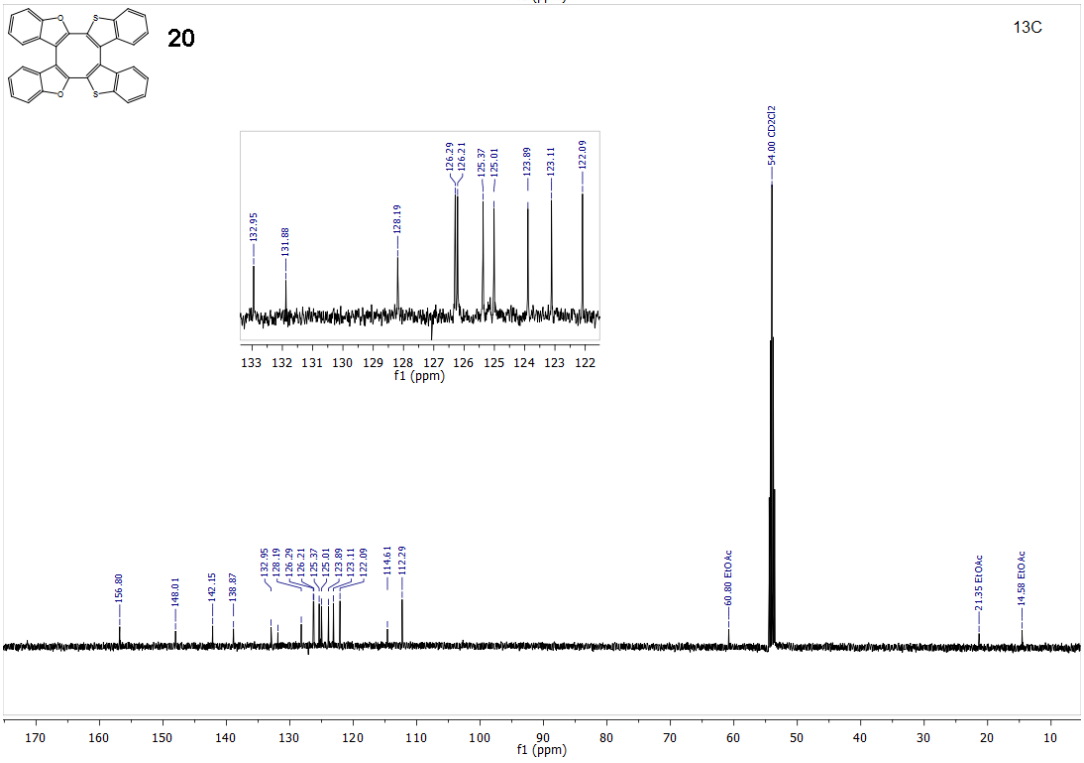

15
HSQC
f2 (ppm)
f1 (ppm)

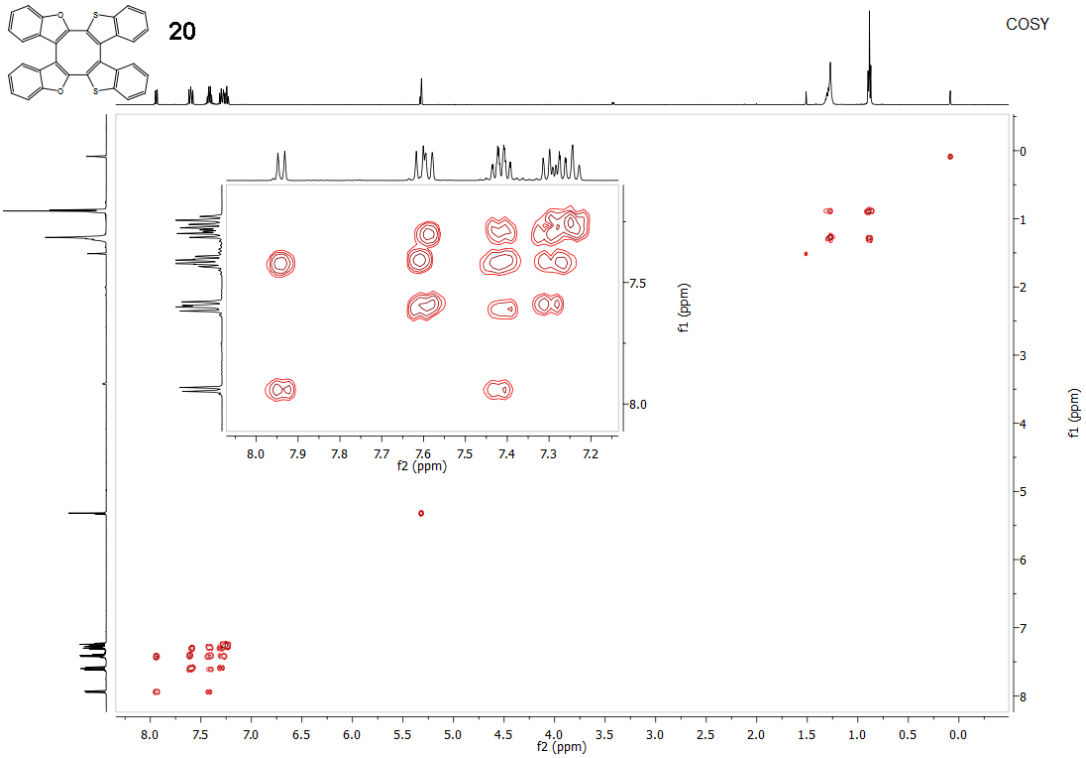

15
HMBC
f2 (ppm)
f1 (ppm)

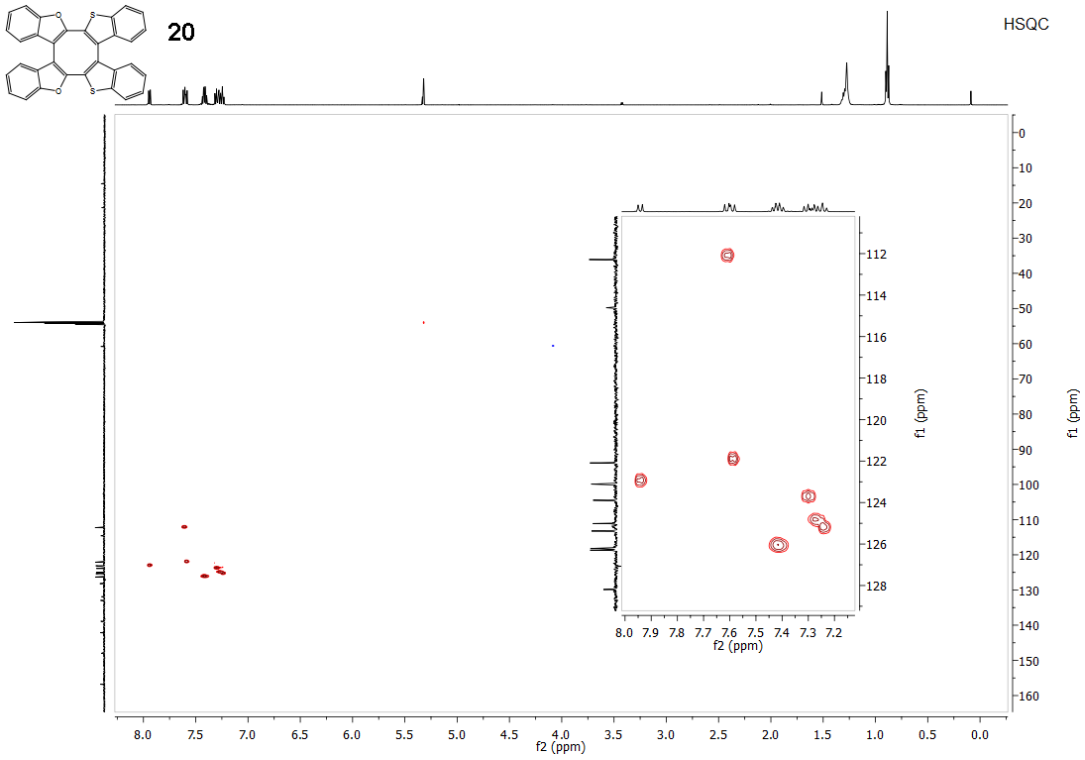

16
1H
A (d)
7.63
B (d)
7.56
C (dd)
7.43
D (t)
7.31
7.64
7.63
7.57
7.55
7.44
7.43
7.41
7.32
7.31
7.30
7.29
7.26 CDCl3
1.94
2.00
1.98
1.99
f1 (ppm)

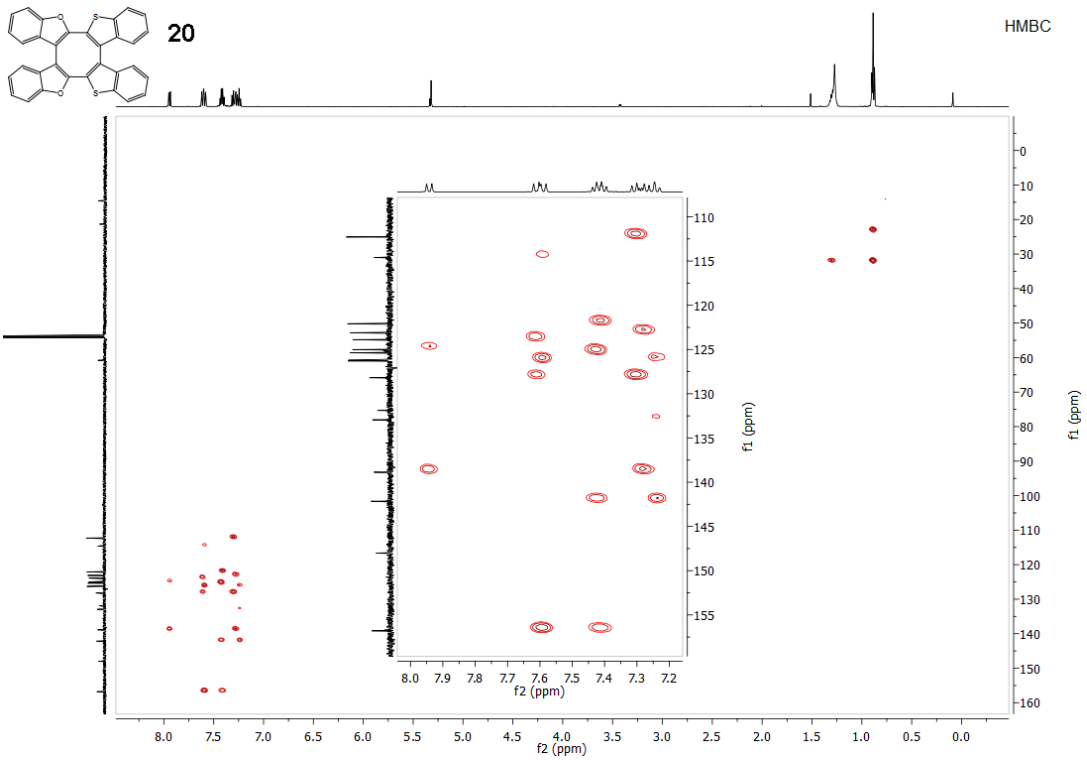

16
13C
77.2 CDCl3
157.0
148.4
127.3
126.4
123.6
122.1
115.6
112.2
f1 (ppm)

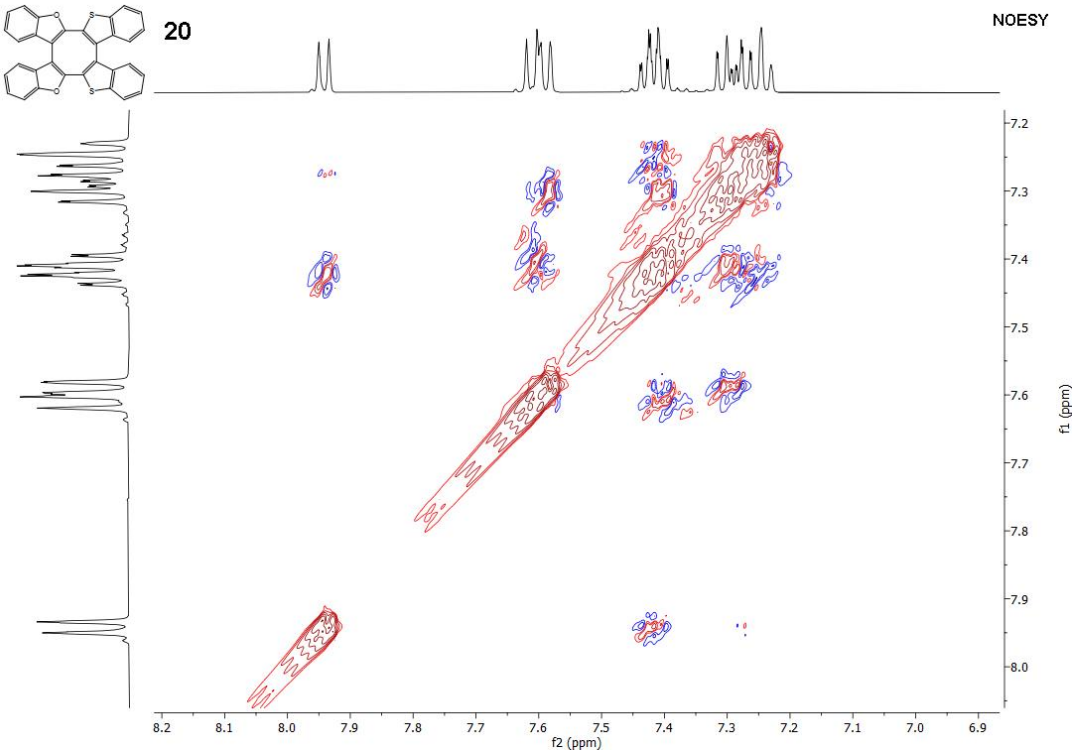

20
1H
A (d) 7.94
B (d) 7.61
C (d) 7.59
D (m) 7.42
E (m) 7.27
f1 (ppm)
5.32 CD2Cl2
1.27 nHex
0.89 nHex

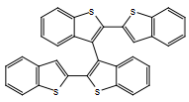

20
13C
132.95
131.88
128.19
126.29
126.21
125.37
125.01
123.89
123.11
122.09
54.00 CD2Cl2
156.80
148.01
142.15
138.87
114.61
112.29
60.80 EtOAc
21.35 EtOAc
14.58 EtOAc
f1 (ppm)


20
COSY
f2 (ppm)
f1 (ppm)


20
HSQC
f2 (ppm)
f1 (ppm)

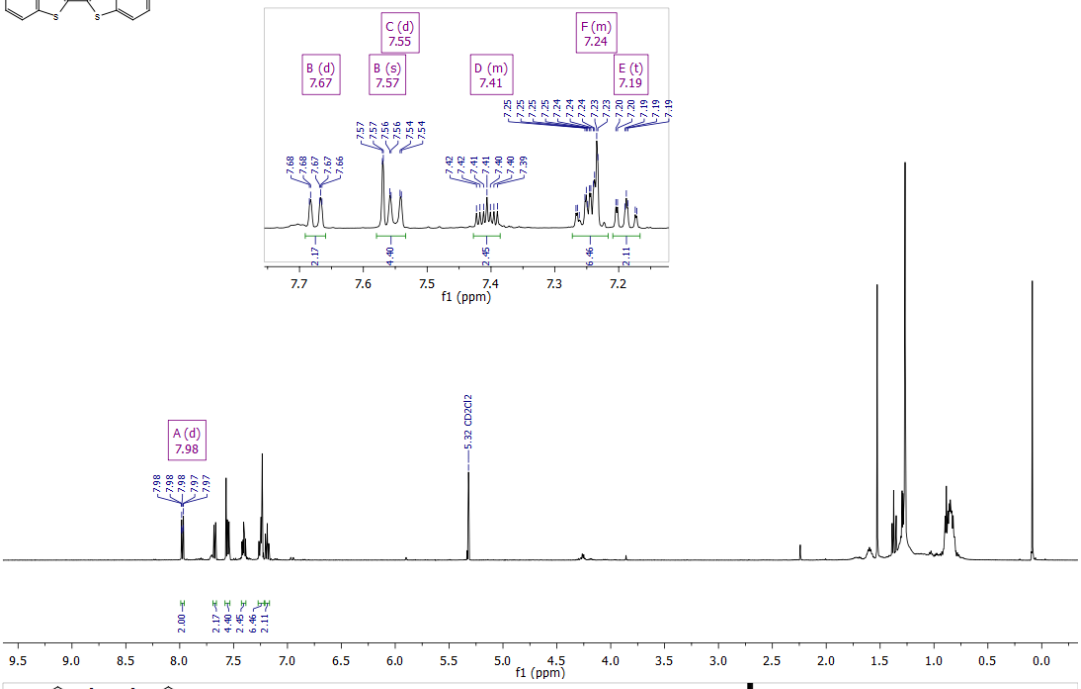

20
HMBC
f2 (ppm)
f1 (ppm)

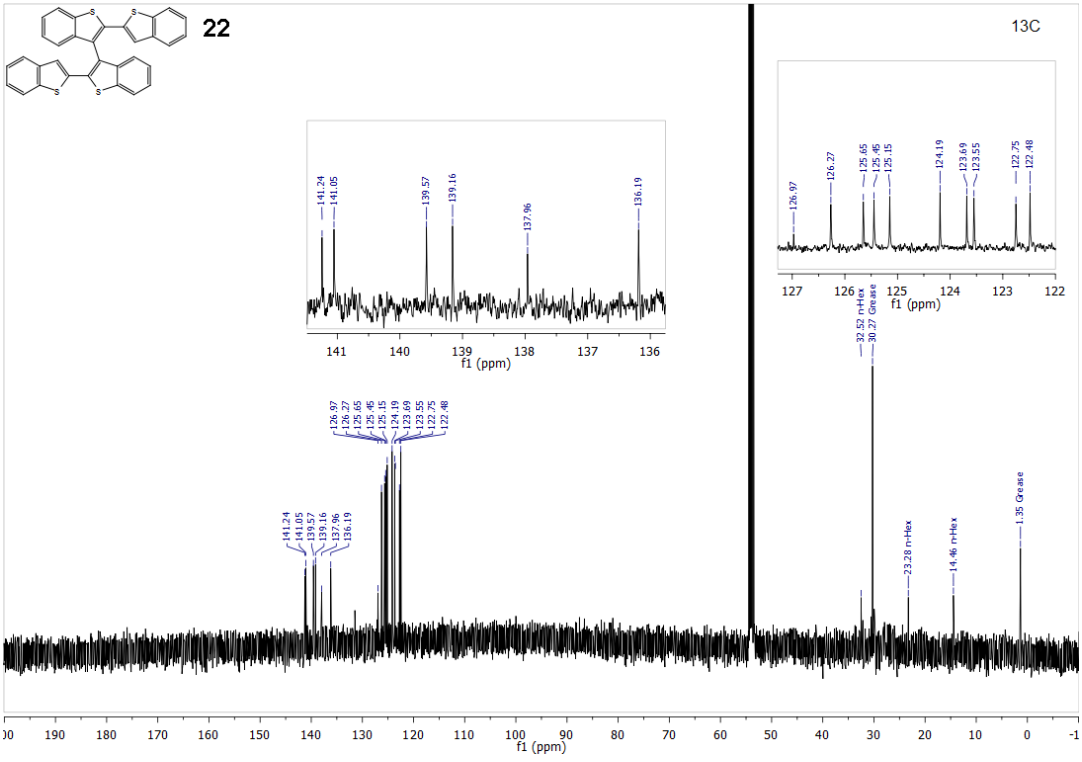

20
NOESY
f2 (ppm)
f1 (ppm)

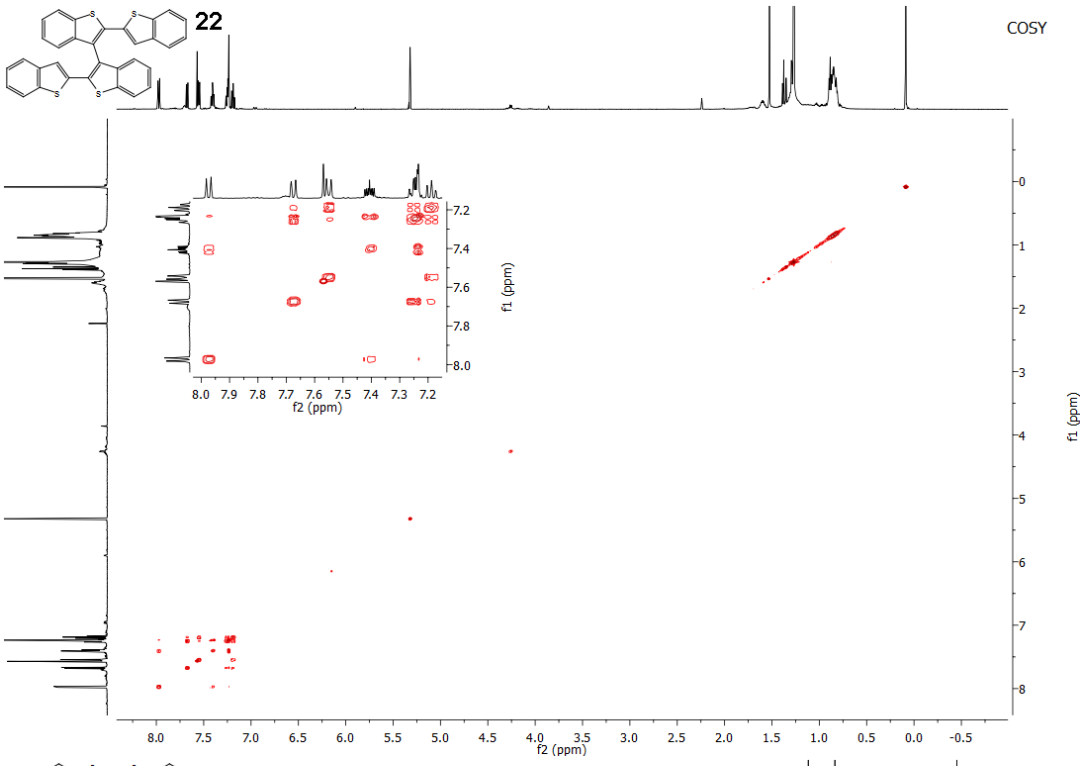


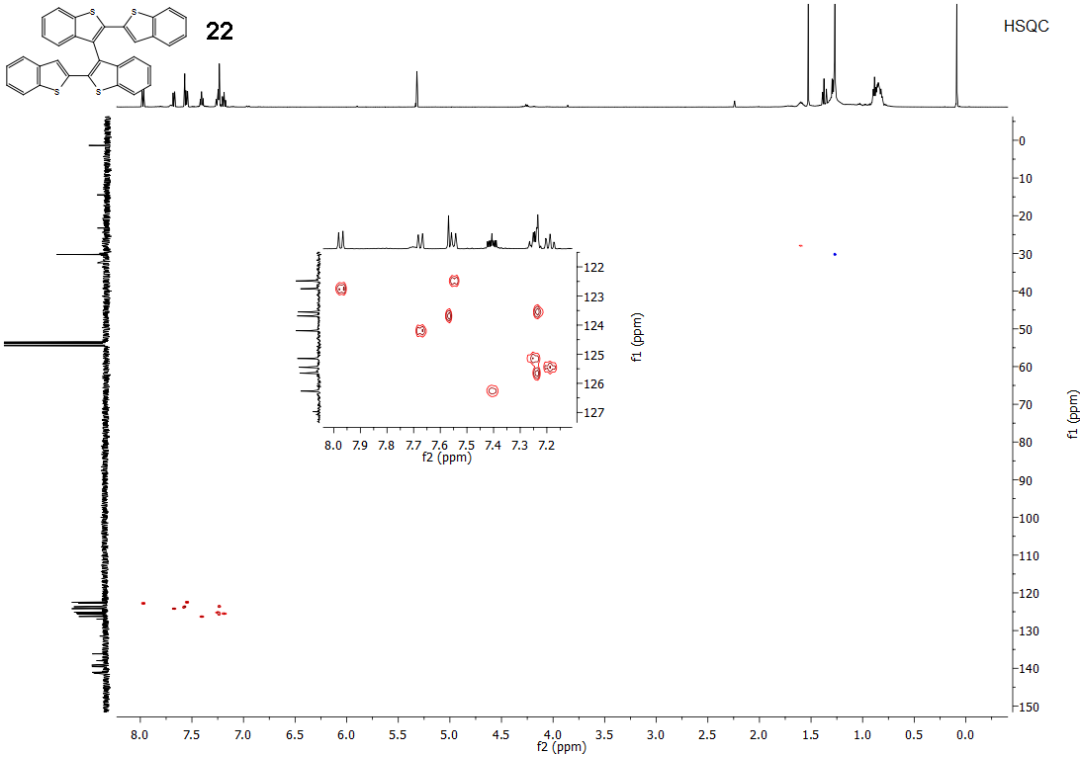
22

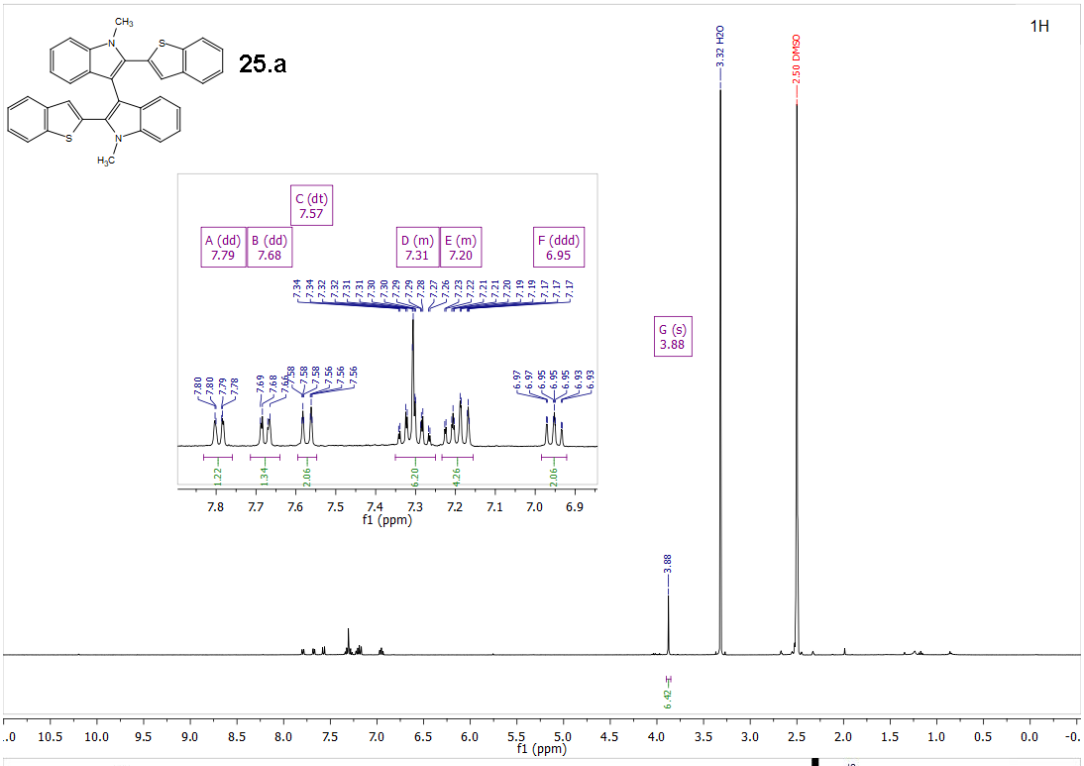
1H

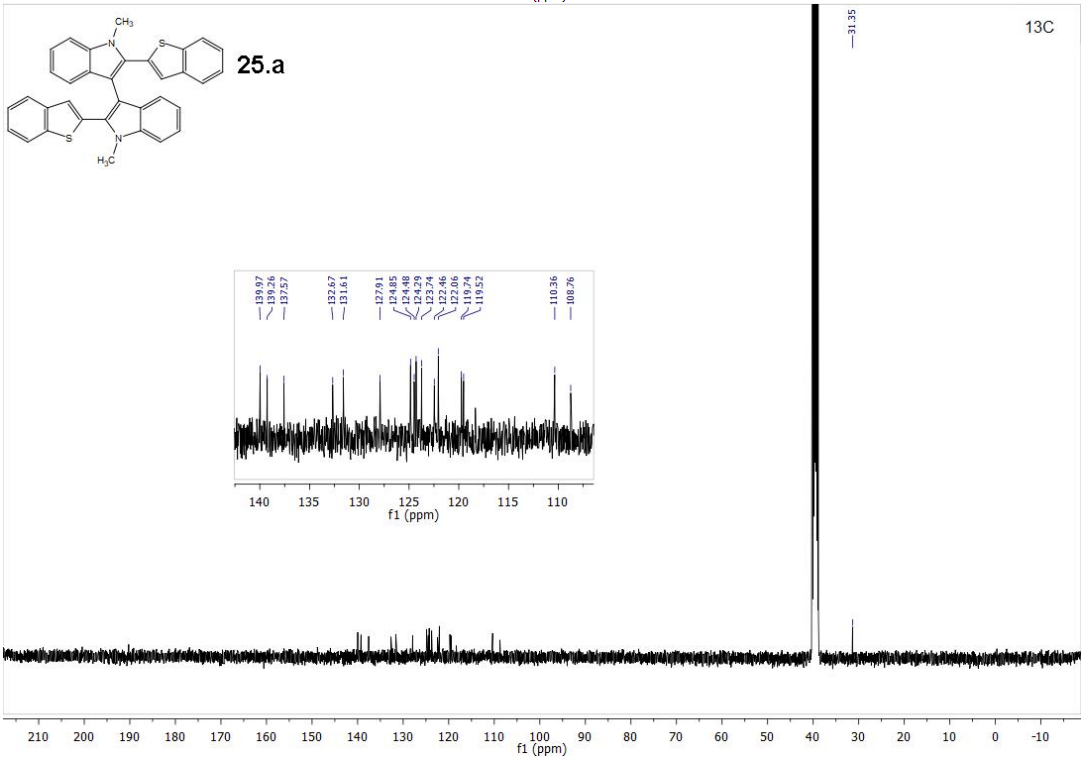

A (d)
7.98
B (d)
7.67
B (s)
7.57
C (d)
7.55
D (m)
7.41
E (t)
7.19
F (m)
7.24
5.32 CD2Cl2
f1 (ppm)

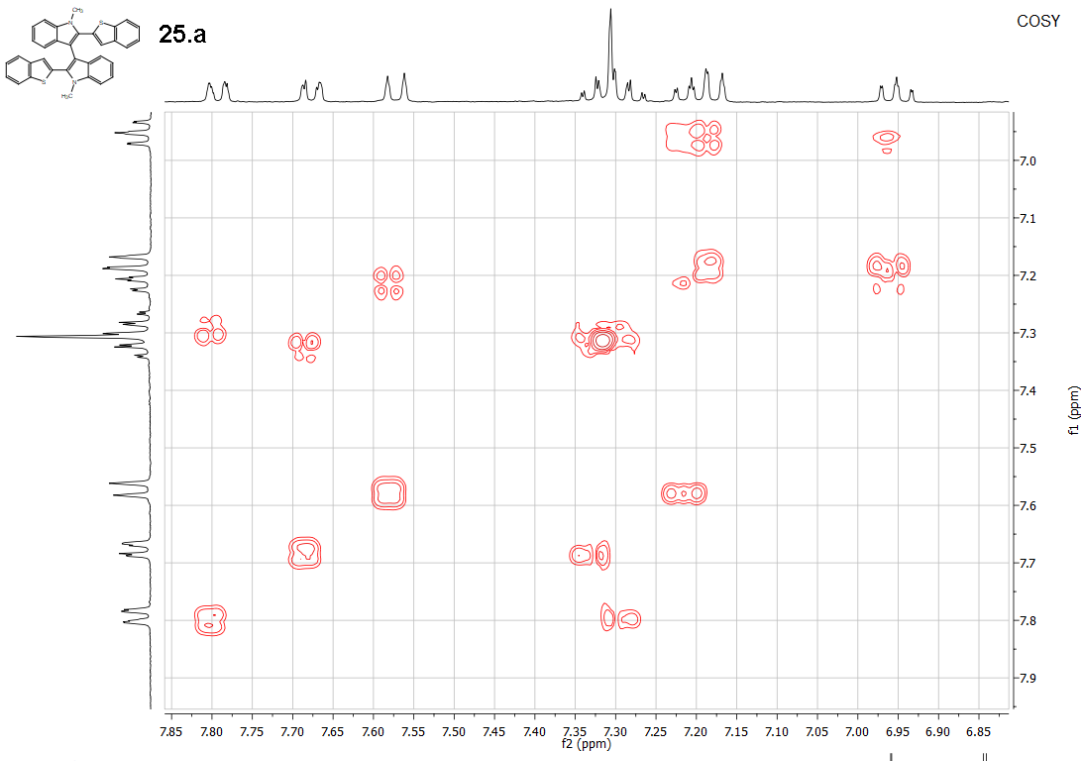

22
13C
141.24
141.05
139.57
139.16
137.96
136.19
126.97
126.27
125.65
125.45
125.15
124.19
123.69
123.55
122.75
122.48
32.52 n-Hex
30.27 Grease
23.28 n-Hex
14.46 n-Hex
1.35 Grease
f1 (ppm)

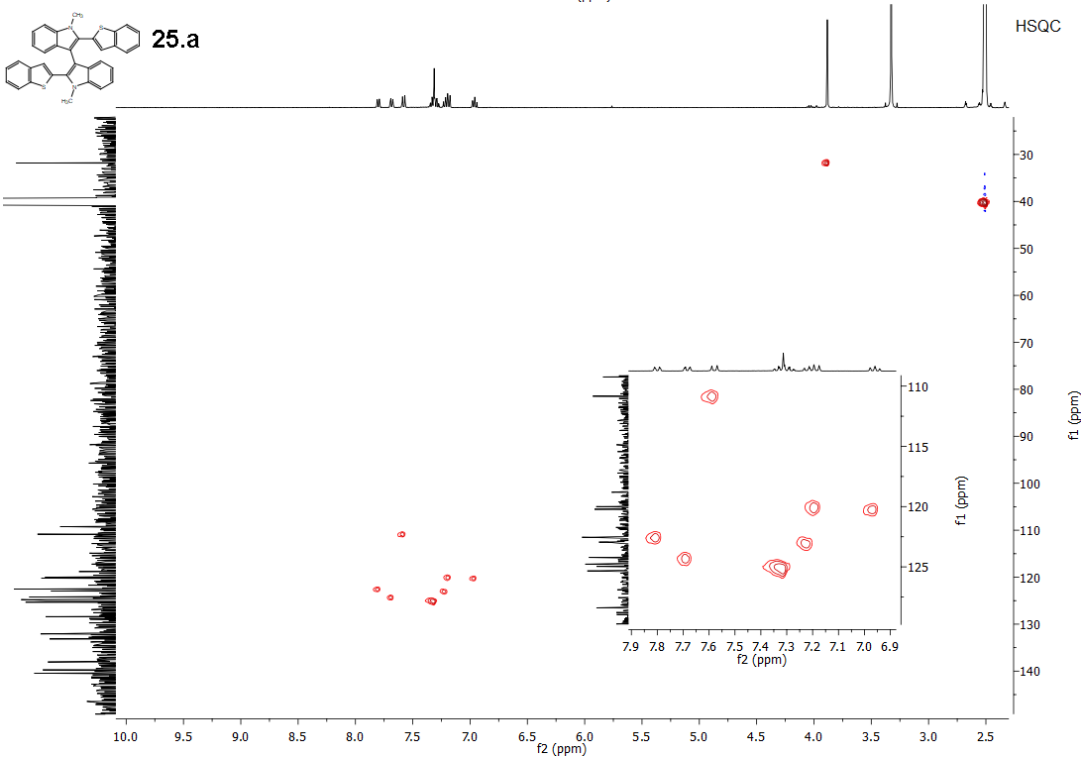

22
COSY
f2 (ppm)
f1 (ppm)

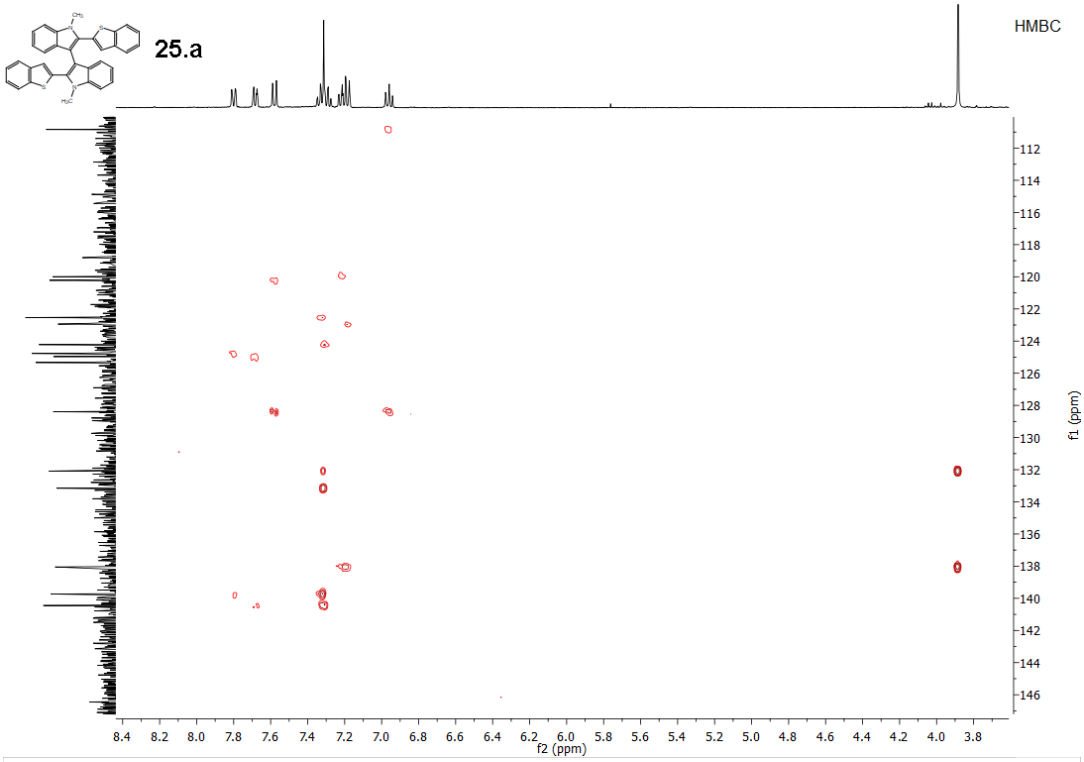

22
HSQC
f2 (ppm)
f1 (ppm)

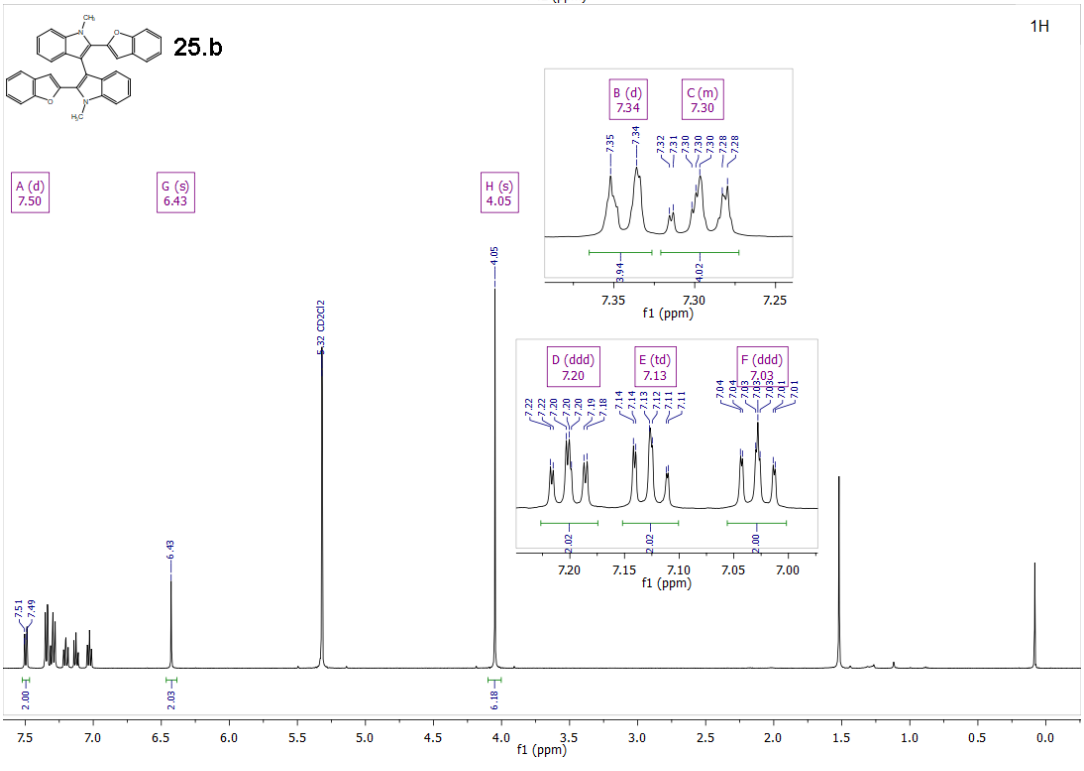

25.a
1H
3.32 H2O
2.50 DMSO
C (dt) 7.57
A (dd) 7.79
B (dd) 7.68
D (m) 7.31
E (m) 7.20
F (ddd) 6.95
G (s) 3.88
f1 (ppm)

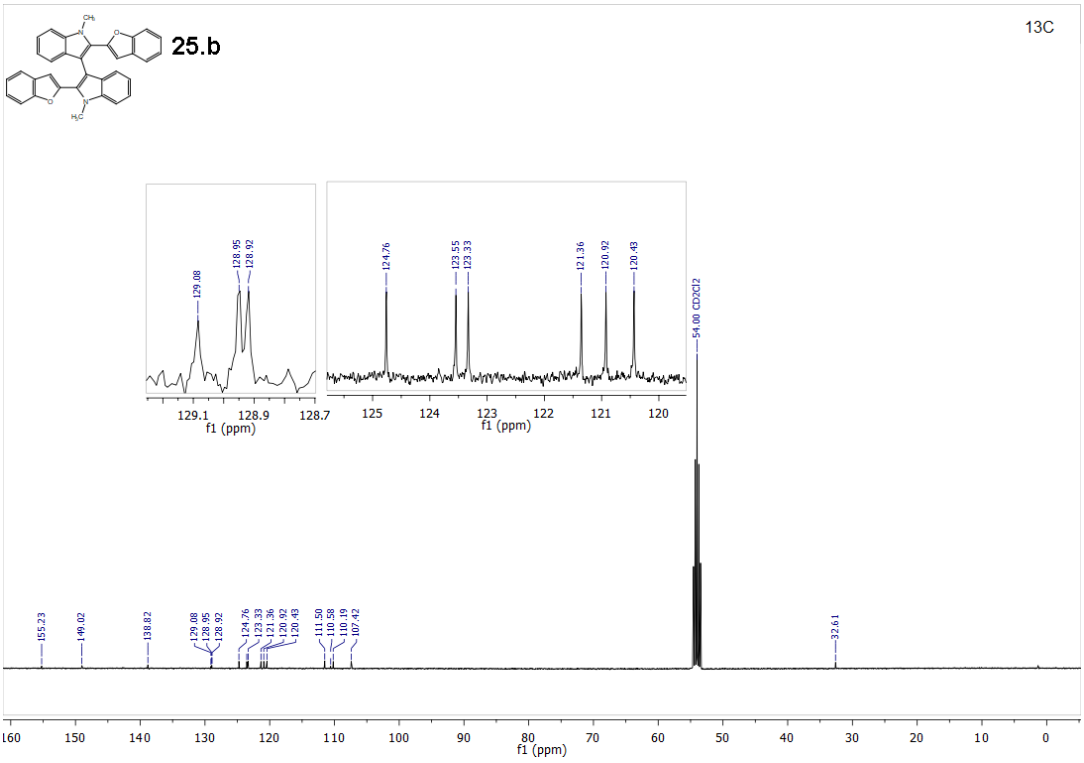

25.a
13C
31.35
f1 (ppm)

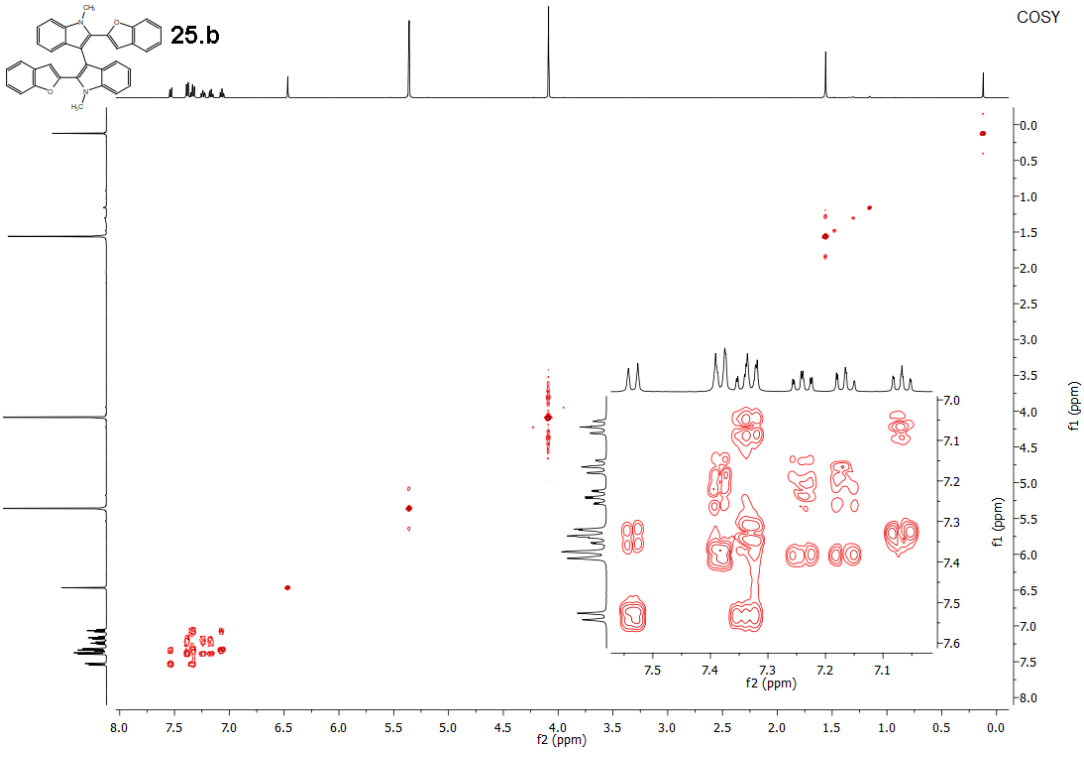

25.a
COSY
f1 (ppm)
f2 (ppm)

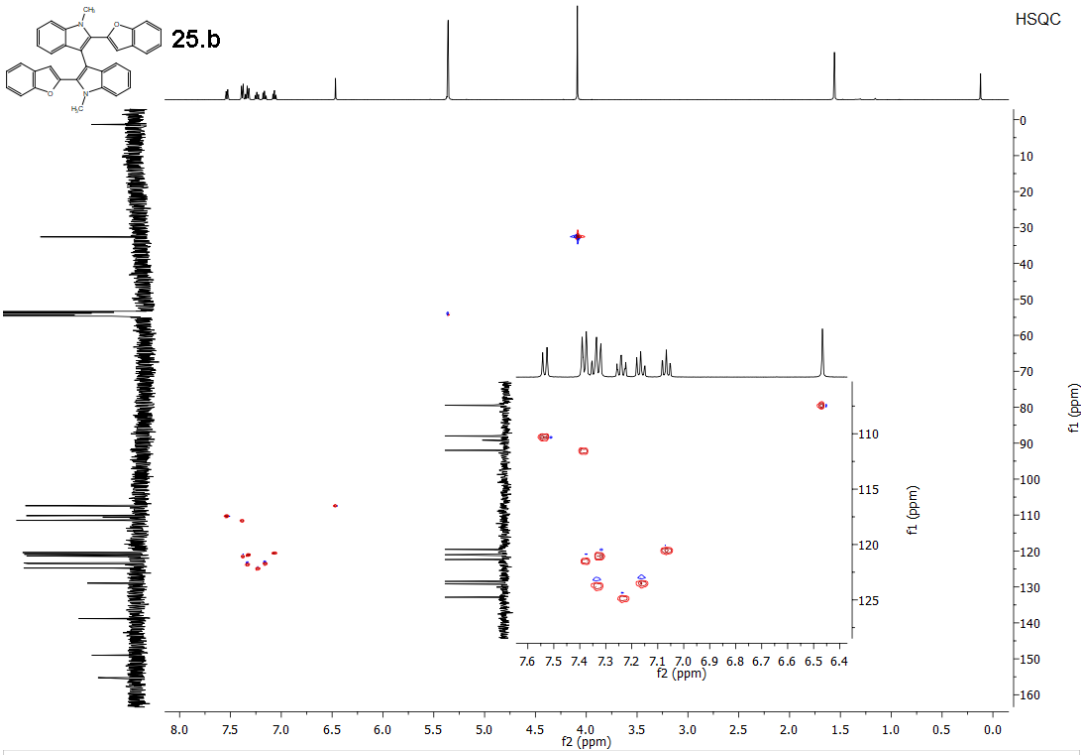

25.a
HSQC
f1 (ppm)
f2 (ppm)

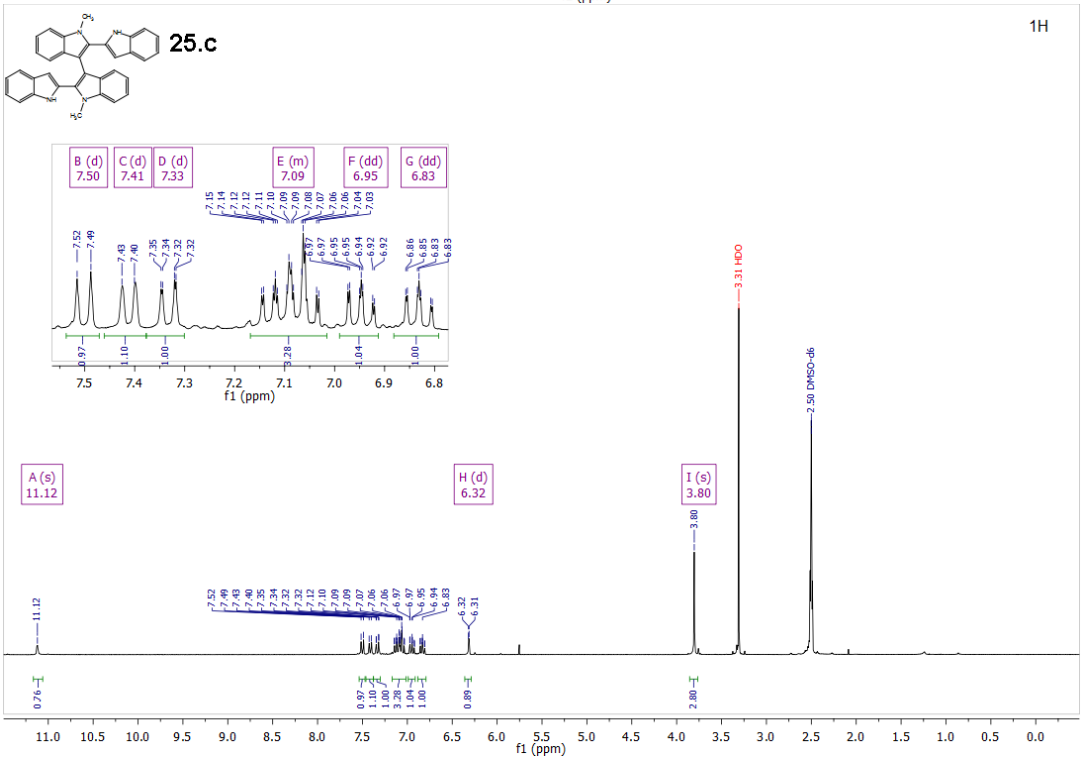

25.a
HMBC
f2 (ppm)
f1 (ppm)

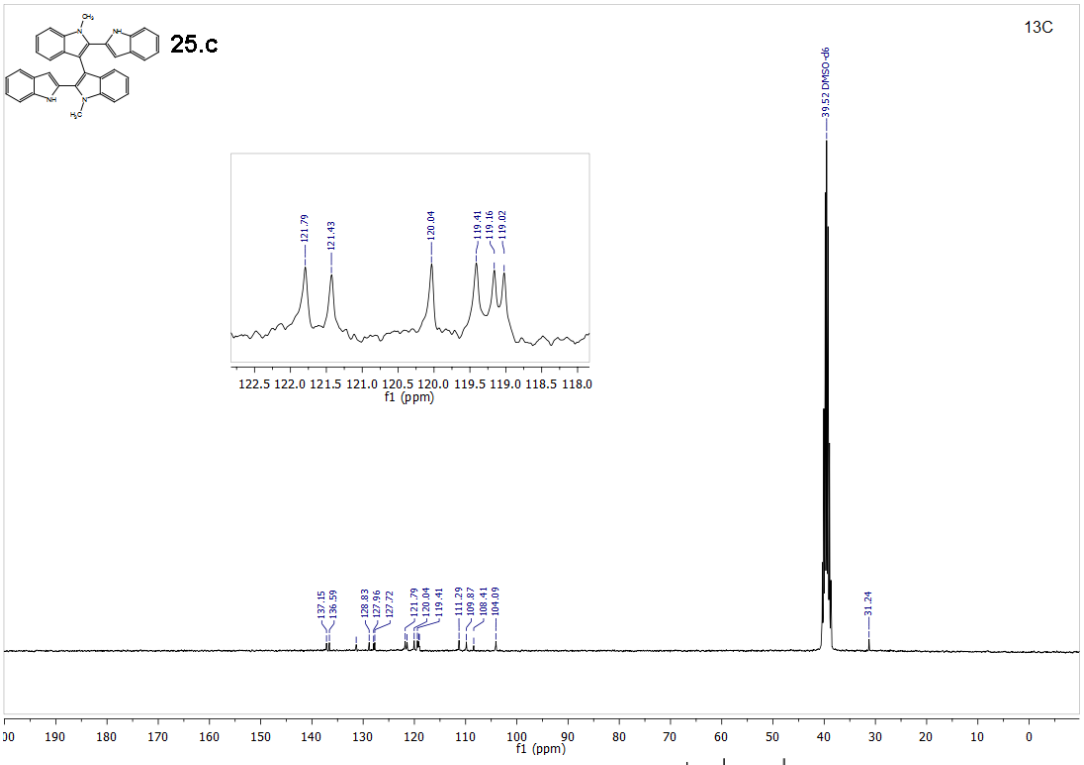

25.b
1H
A (d)
7.50
G (s)
6.43
H (s)
4.05
B (d)
7.34
C (m)
7.30
D (ddd)
7.20
E (td)
7.13
F (ddd)
7.03
f1 (ppm)

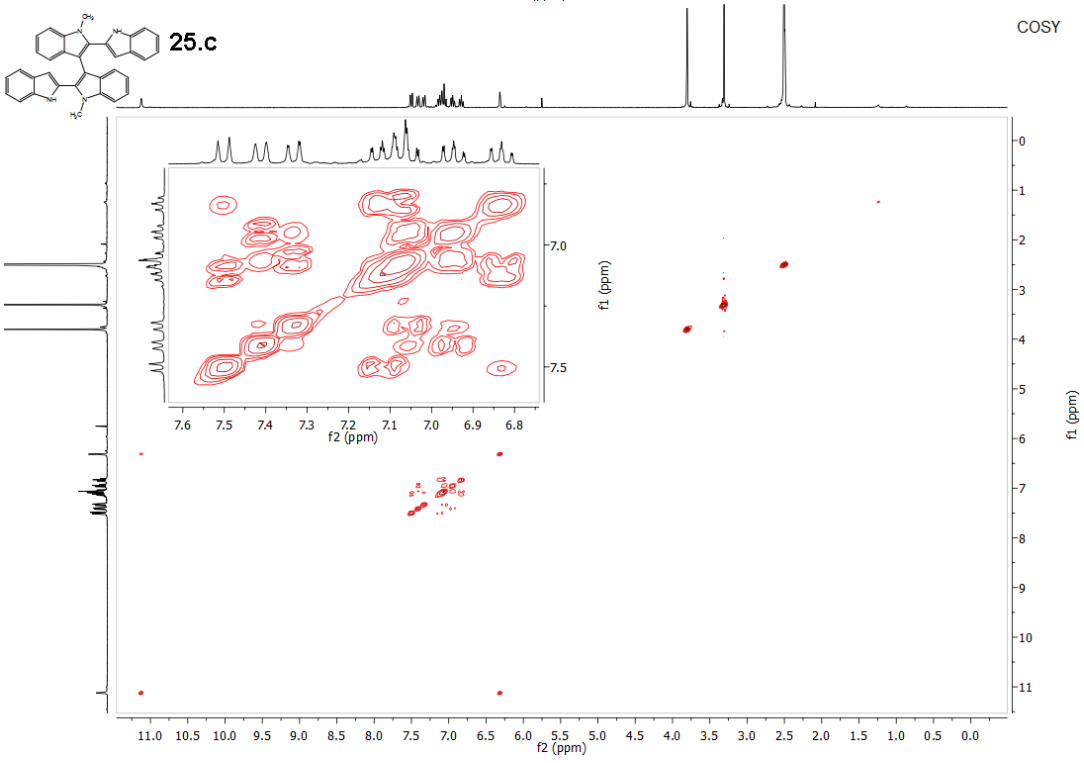

25.b
13C
129.08
128.95
128.92
124.76
123.55
123.33
121.36
120.92
120.43
54.00 CD2Cl2
155.23
149.02
138.82
111.50
110.58
110.19
107.42
32.61
f1 (ppm)

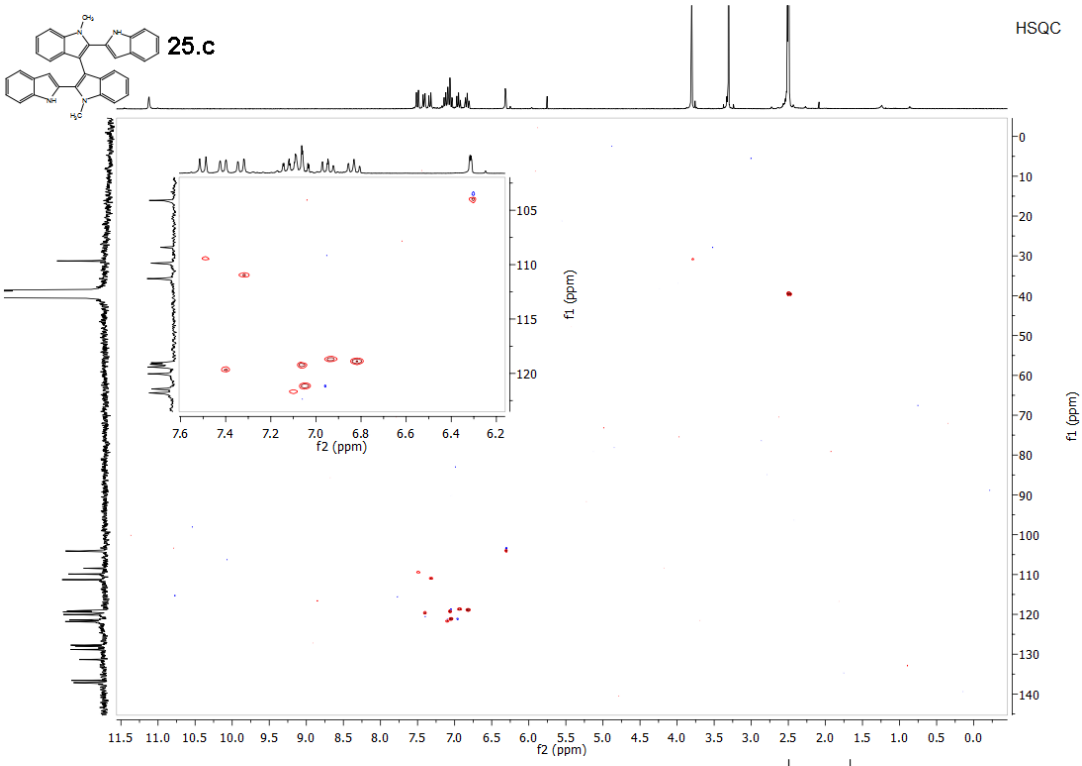

25.b
COSY
f2 (ppm)
f1 (ppm)

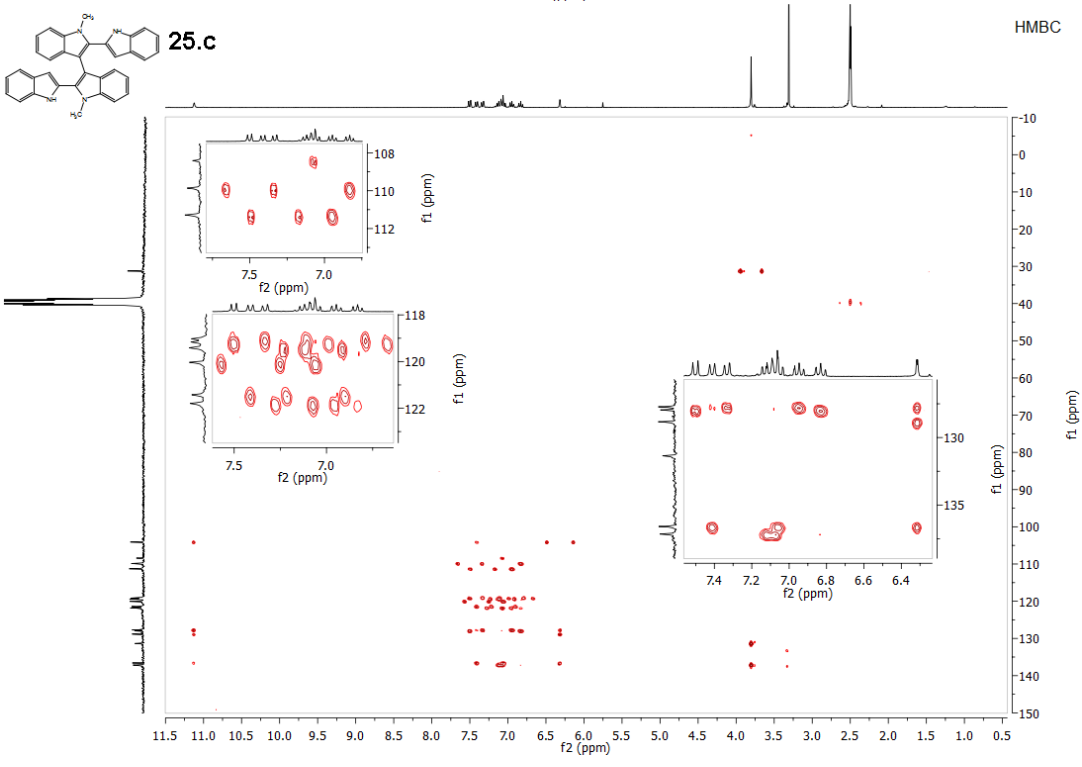

25.b
HSQC
f2 (ppm)
f1 (ppm)

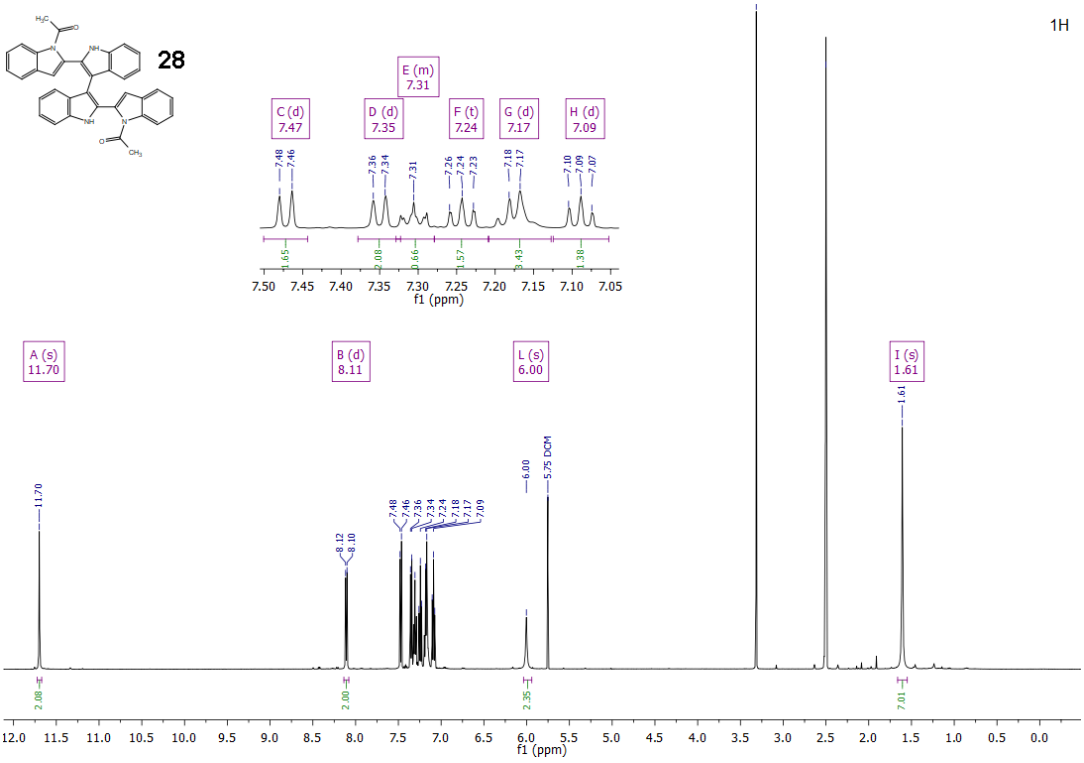

25.c
1H
B (d) 7.50
C (d) 7.41
D (d) 7.33
E (m) 7.09
F (dd) 6.95
G (dd) 6.83
A (s) 11.12
H (d) 6.32
I (s) 3.80
3.31 HDO
2.50 DMSO-d6
f1 (ppm)

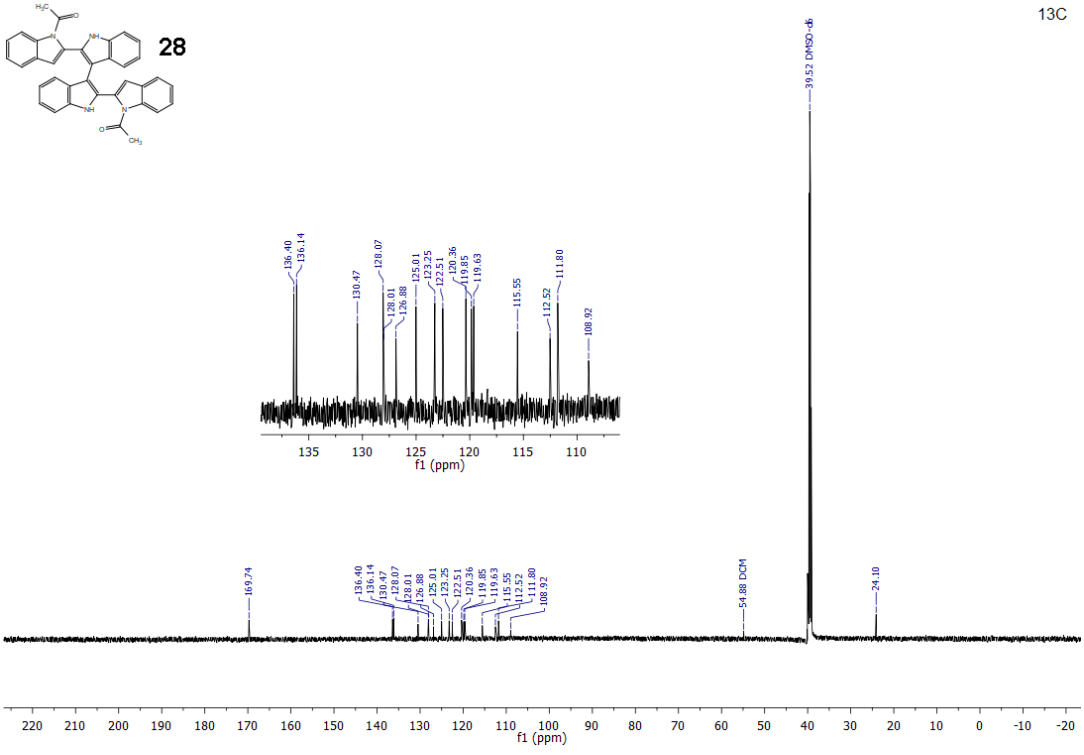

25.c
13C
39.52 DMSO-d6
121.79
121.43
120.04
119.41
119.16
119.02
137.15
136.59
128.83
127.96
127.72
121.79
120.04
119.41
111.29
109.87
108.41
104.09
31.24
f1 (ppm)

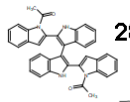

25.c
COSY
f1 (ppm)
f2 (ppm)


25.c
HSQC
f2 (ppm)
f1 (ppm)


25.c
HMBC
f2 (ppm)
f1 (ppm)

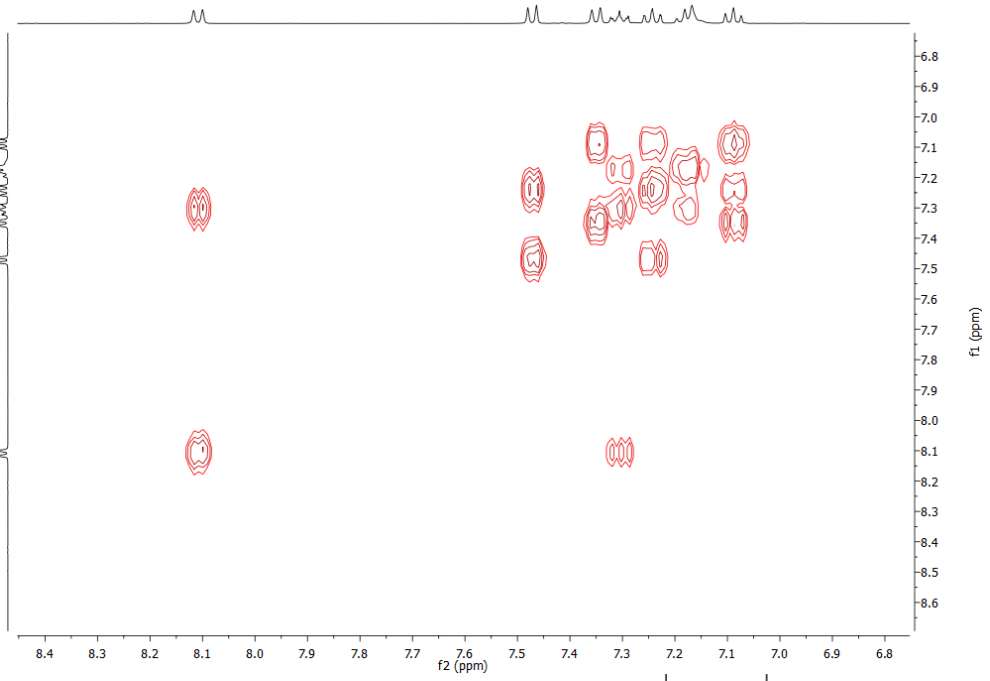

28
1H
A (s) 11.70
B (d) 8.11
L (s) 6.00
I (s) 1.61
C (d) 7.47
D (d) 7.35
E (m) 7.31
F (t) 7.24
G (d) 7.17
H (d) 7.09
f1 (ppm)

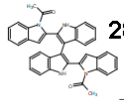

28
13C
f1 (ppm)



28

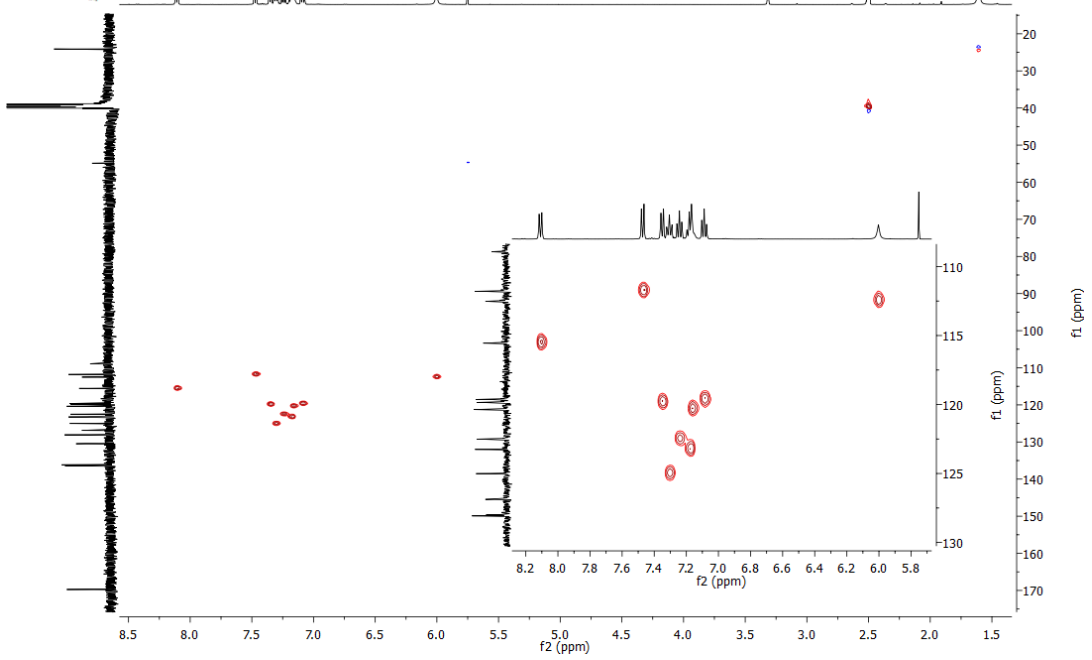
COSY

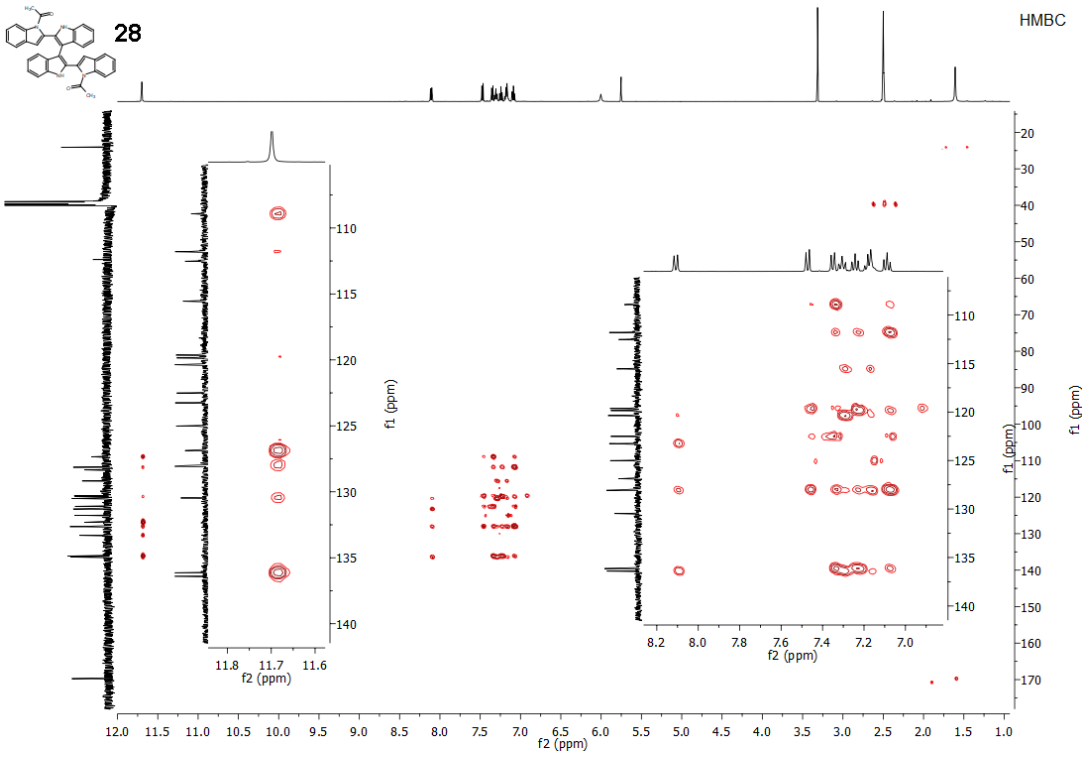


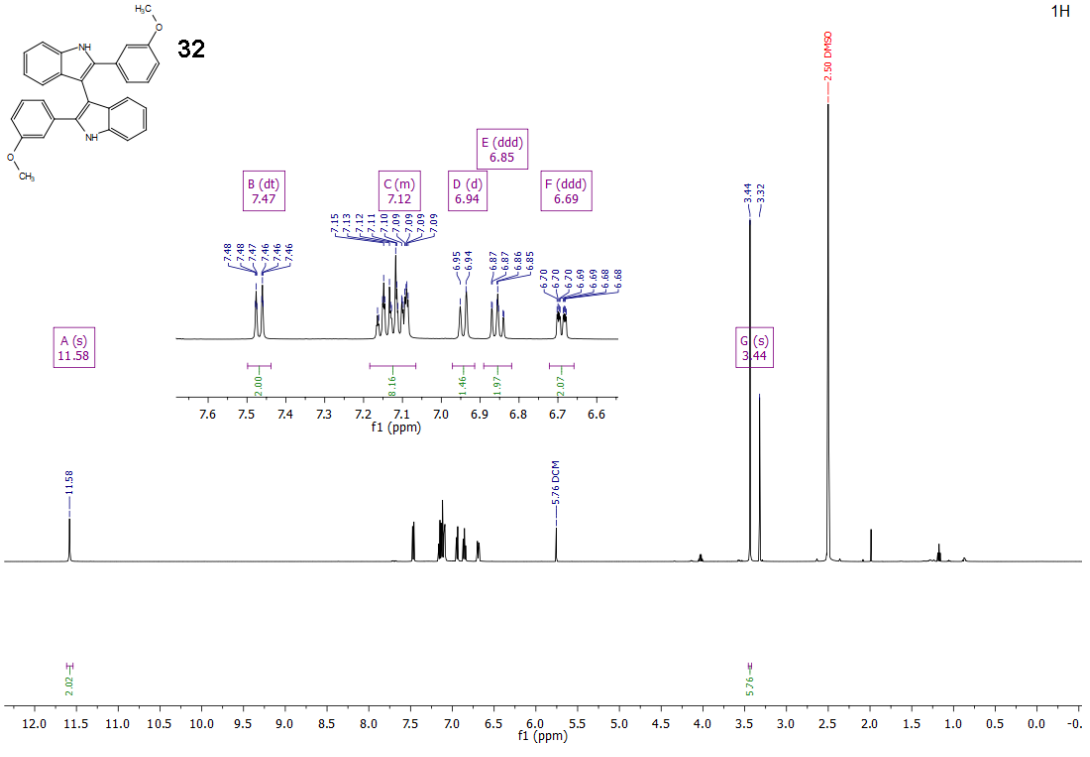


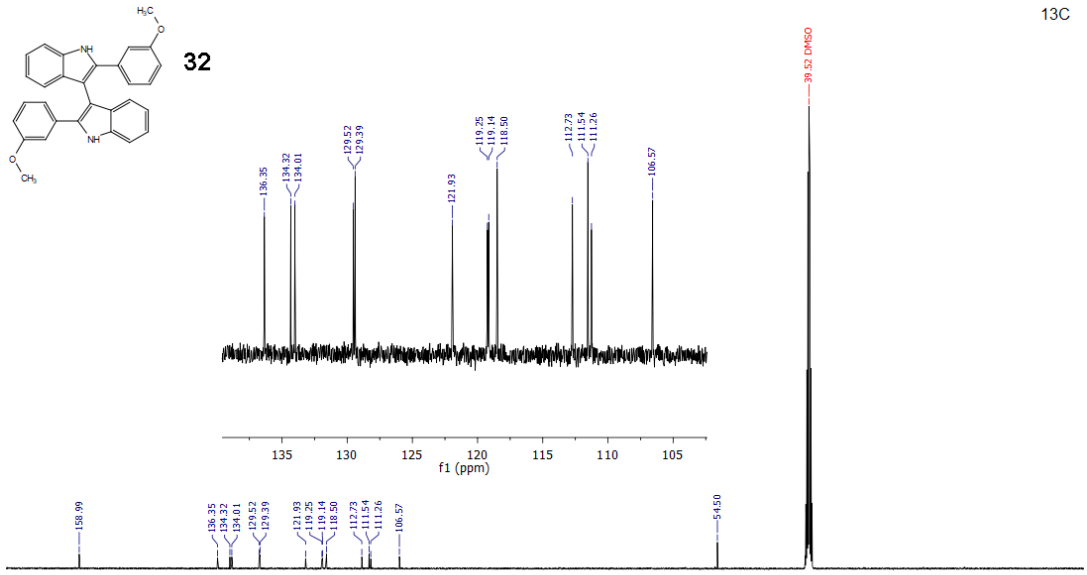
28

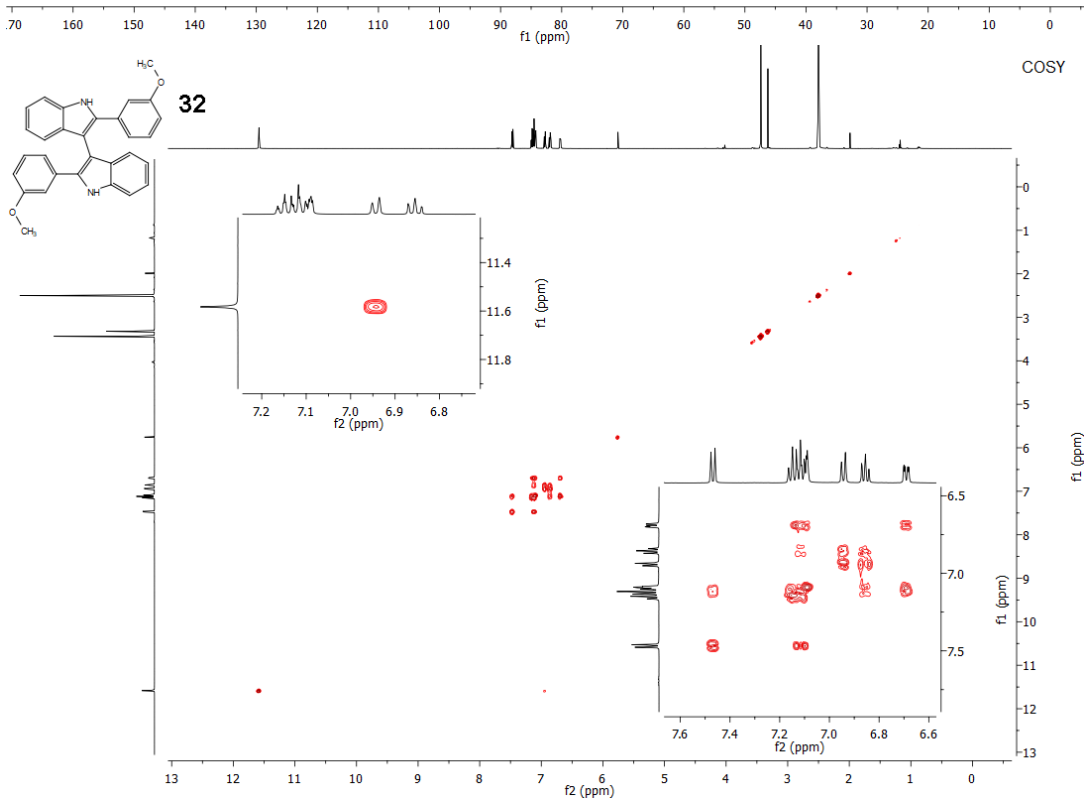
HSQC

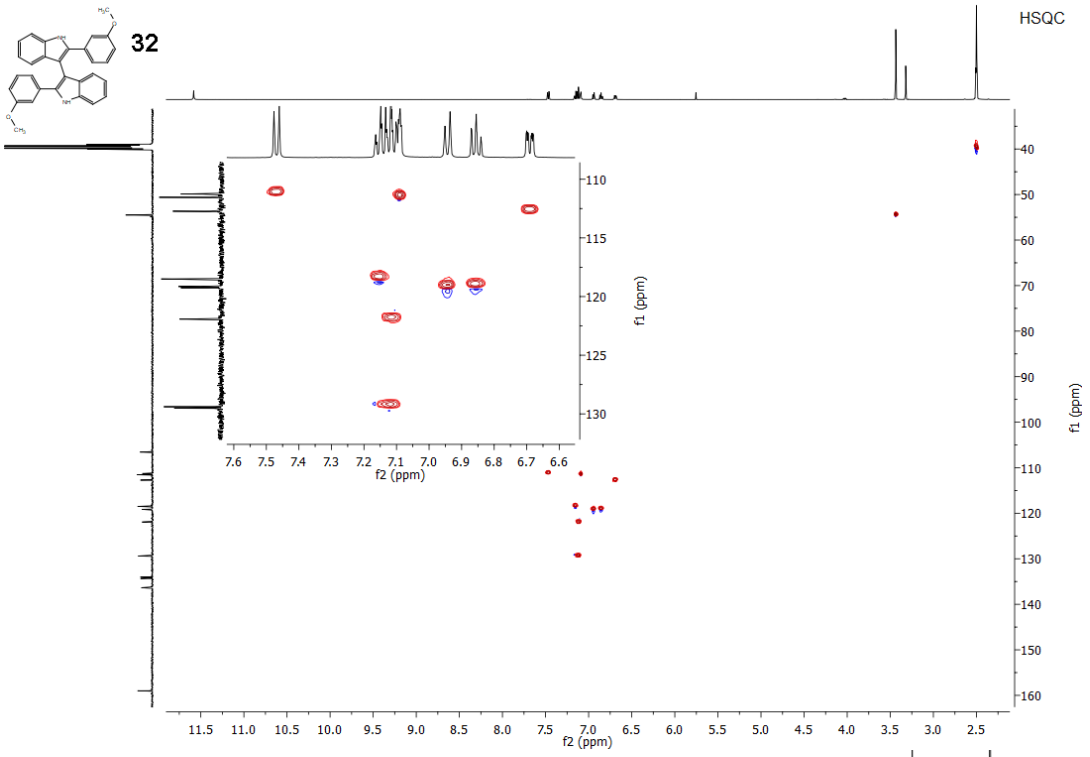


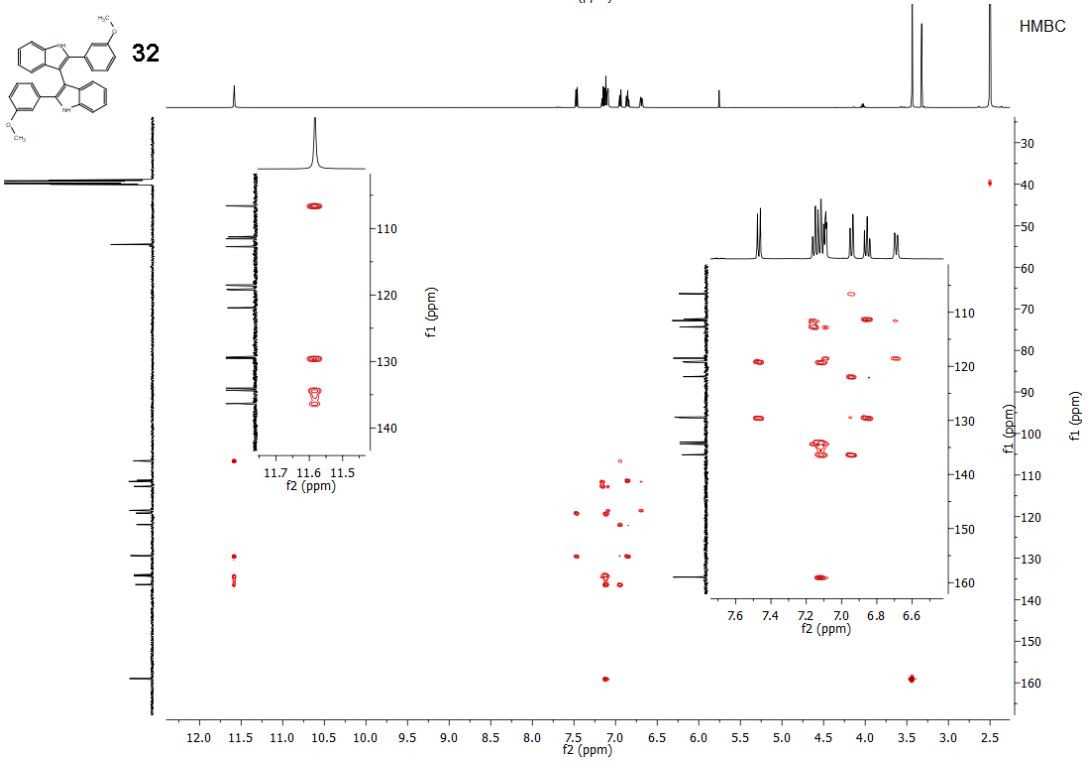

28
HMBC
f1 (ppm)
f2 (ppm)

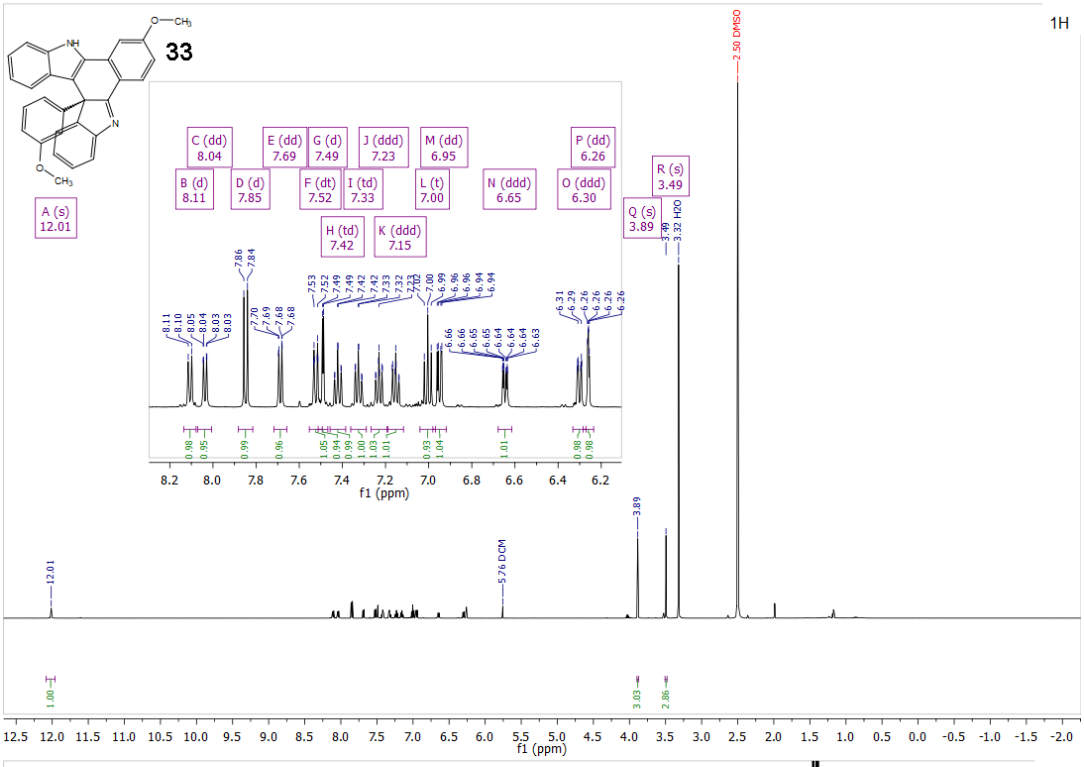

32
1H
A (s)
11.58
B (dt)
7.47
C (m)
7.12
D (d)
6.94
E (ddd)
6.85
F (ddd)
6.69
G (s)
3.44
2.50 DMSO
5.76 DCM
f1 (ppm)

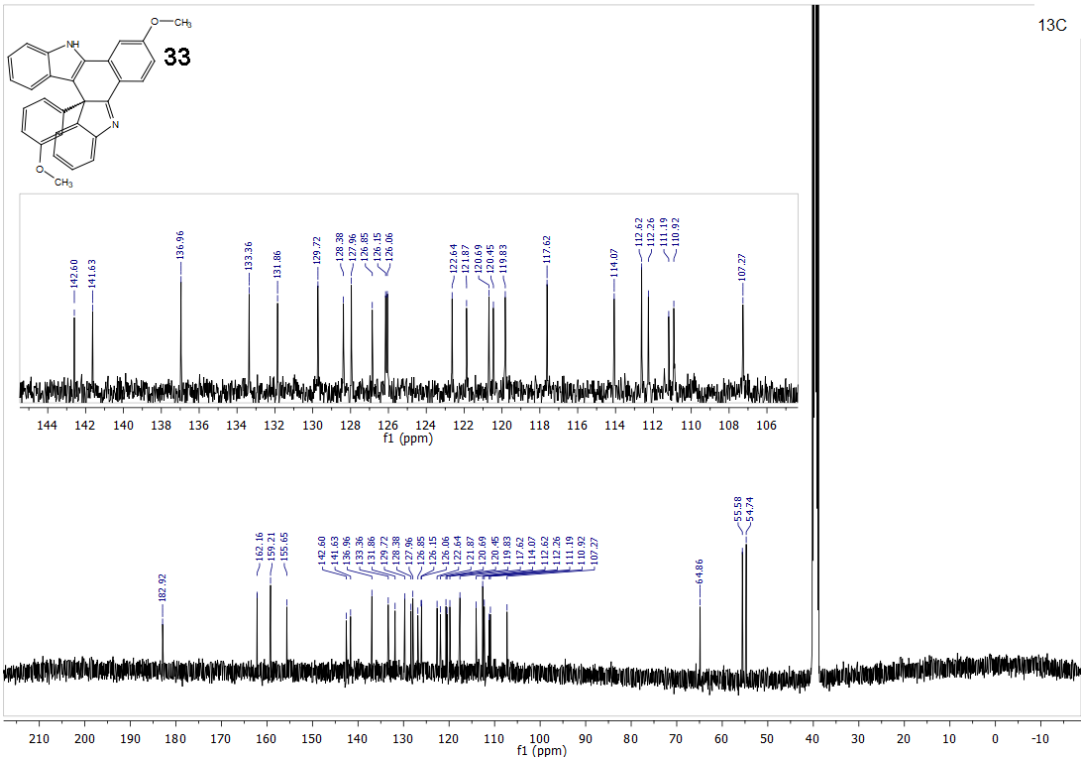

13C
32
39.52 DMSO
136.35
134.32
134.01
129.52
129.39
121.93
119.25
119.14
118.50
112.73
111.54
111.26
106.57
158.99
54.50
f1 (ppm)

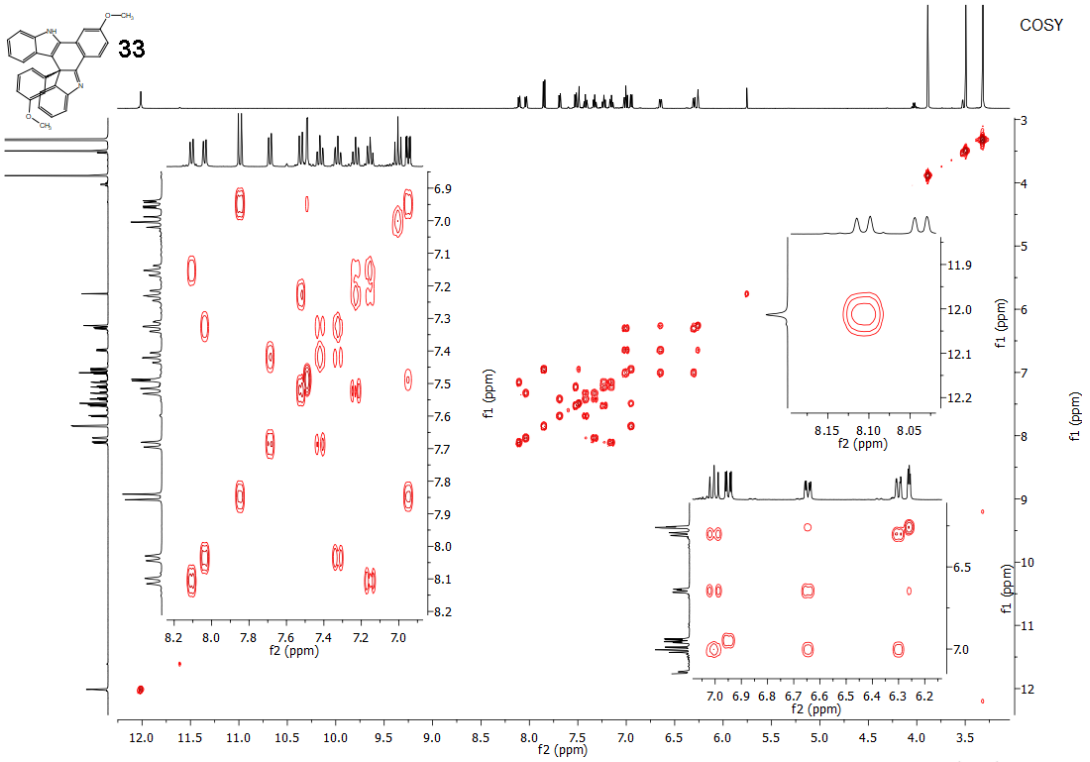

COSY
32
f1 (ppm)
f2 (ppm)

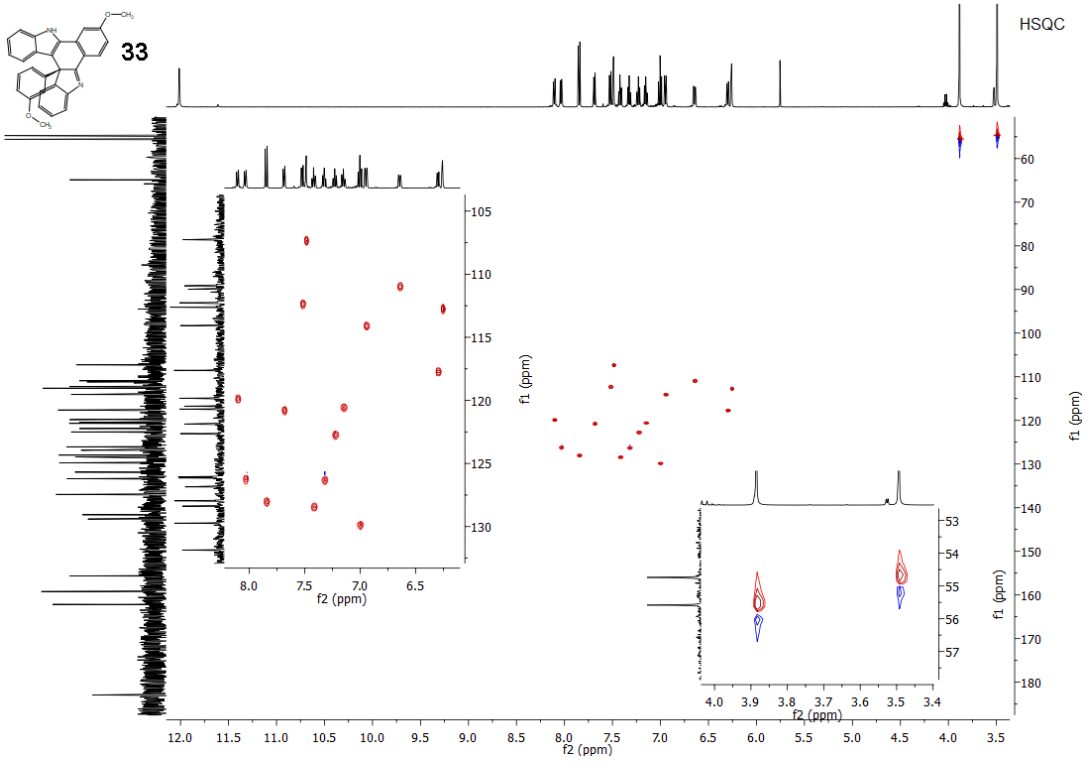

32
HSQC
f1 (ppm)
f2 (ppm)

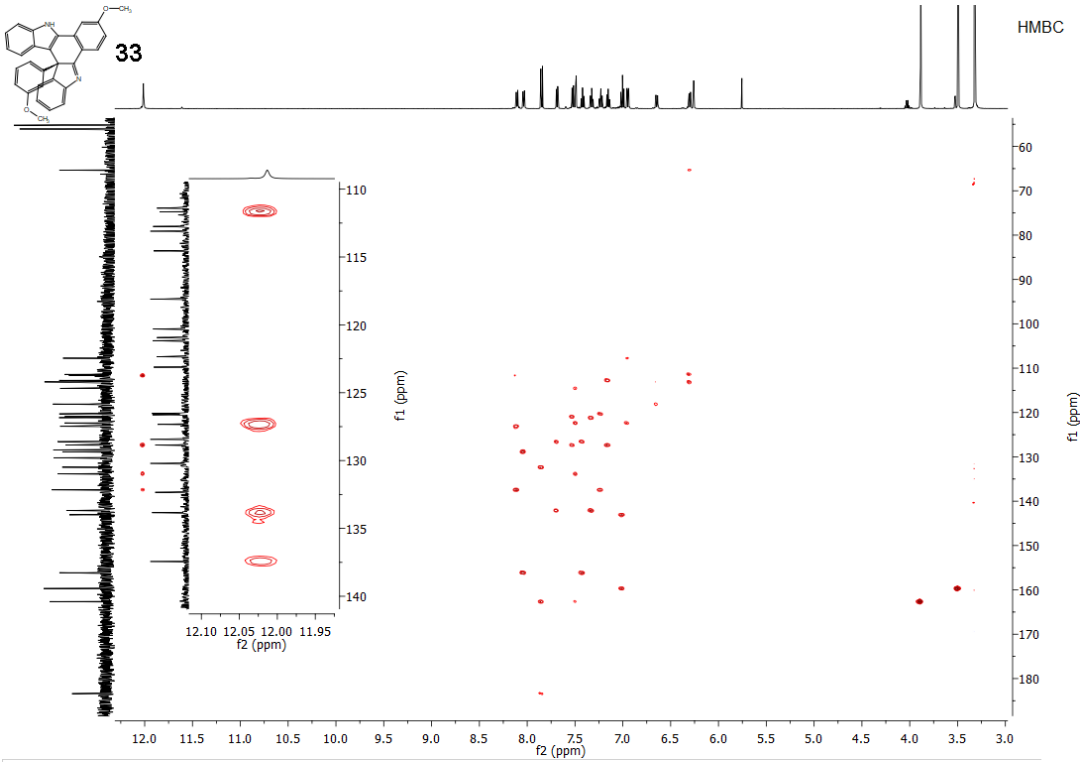

32
HMBC
f1 (ppm)
f2 (ppm)

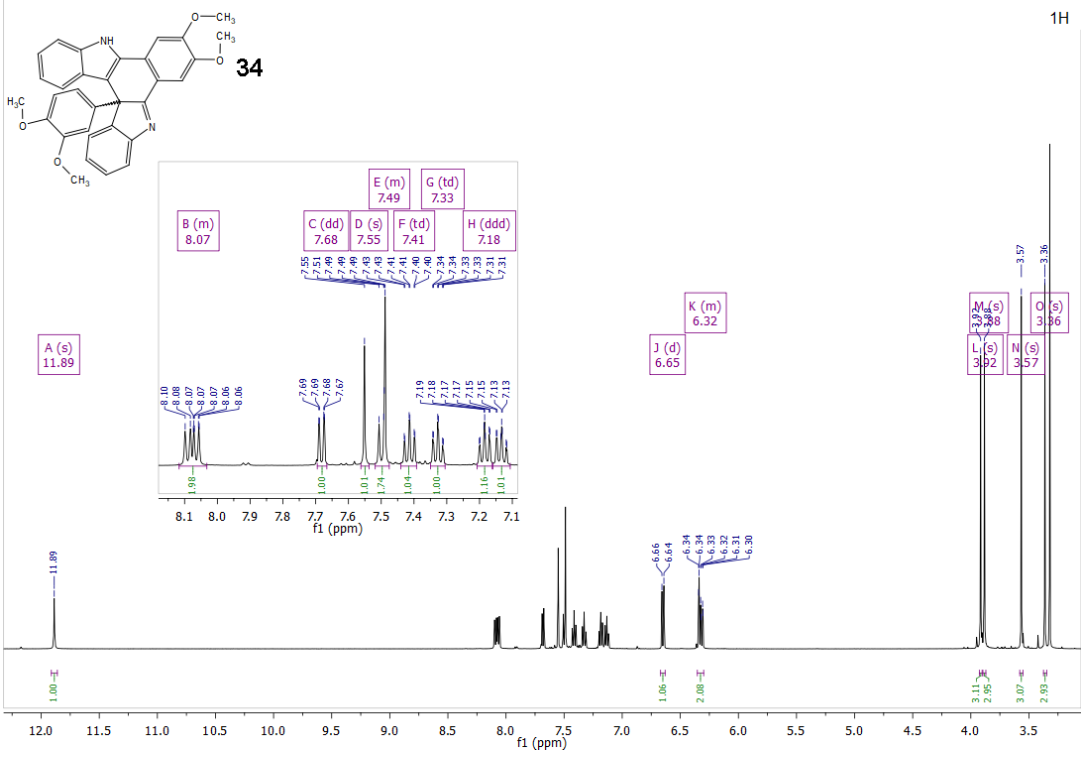

1H
33
A (s) 12.01
B (d) 8.11
C (dd) 8.04
D (d) 7.85
E (dd) 7.69
F (dt) 7.52
G (d) 7.49
H (td) 7.42
I (td) 7.33
J (ddd) 7.23
K (ddd) 7.15
L (t) 7.00
M (dd) 6.95
N (ddd) 6.65
O (ddd) 6.30
P (dd) 6.26
Q (s) 3.89
R (s) 3.49
2.50 DMSO
3.32 H2O
5.76 DCM
f1 (ppm)

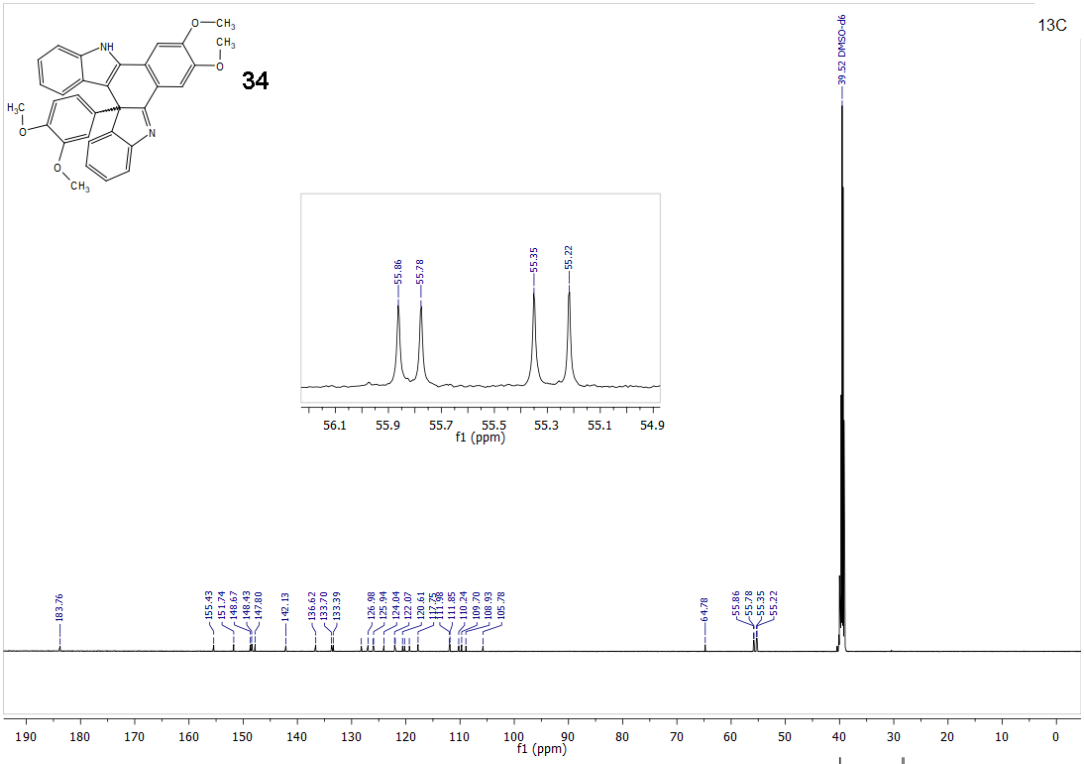

13C
33
f1 (ppm)

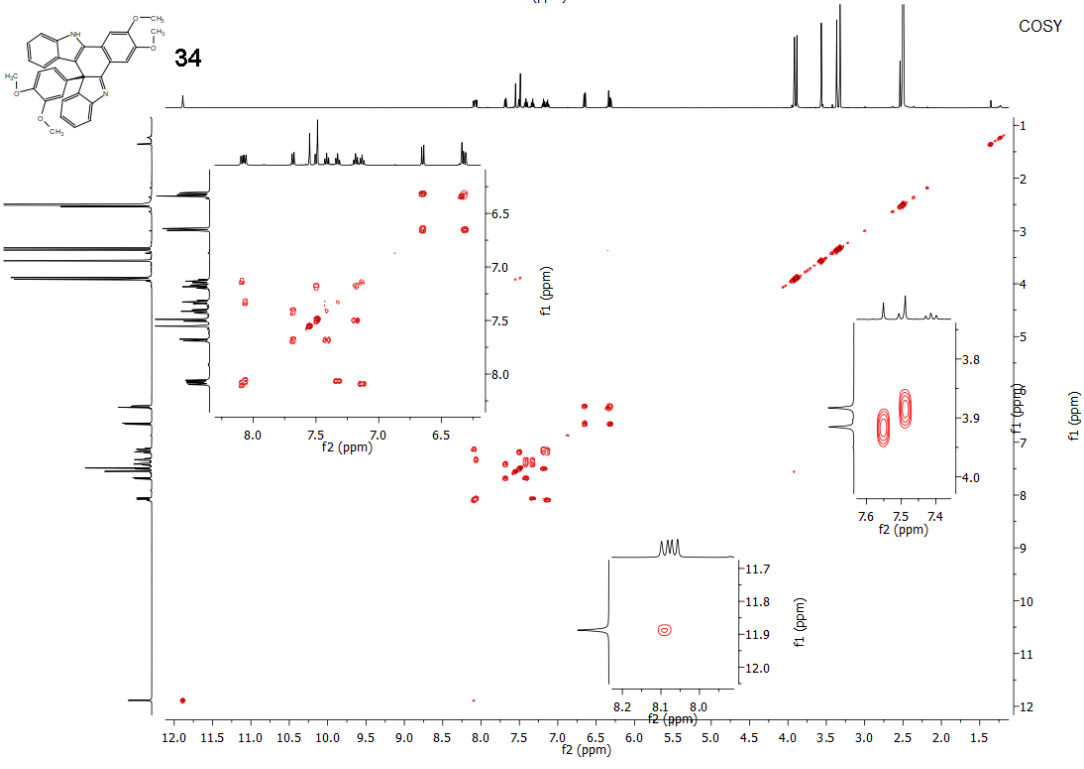

33
COSY
f1 (ppm)
f2 (ppm)

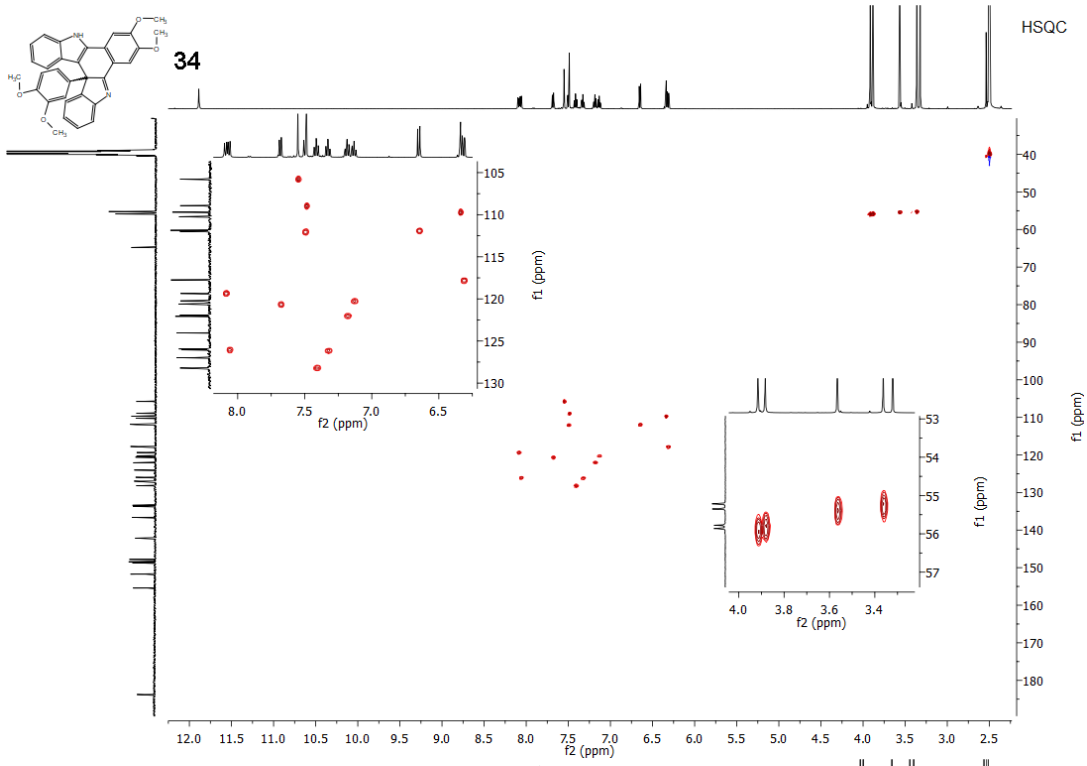

33
HSQC
f1 (ppm)
f2 (ppm)

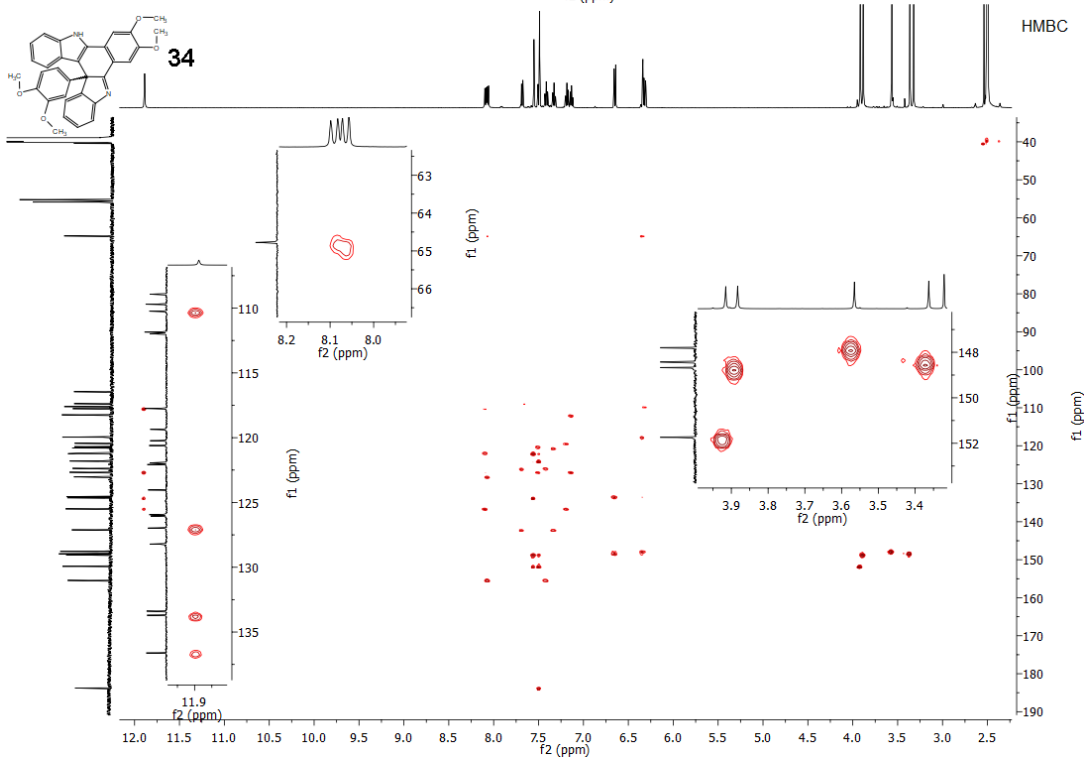

33
HMBC
f1 (ppm)
f2 (ppm)
12.10 12.05 12.00 11.95
f2 (ppm)

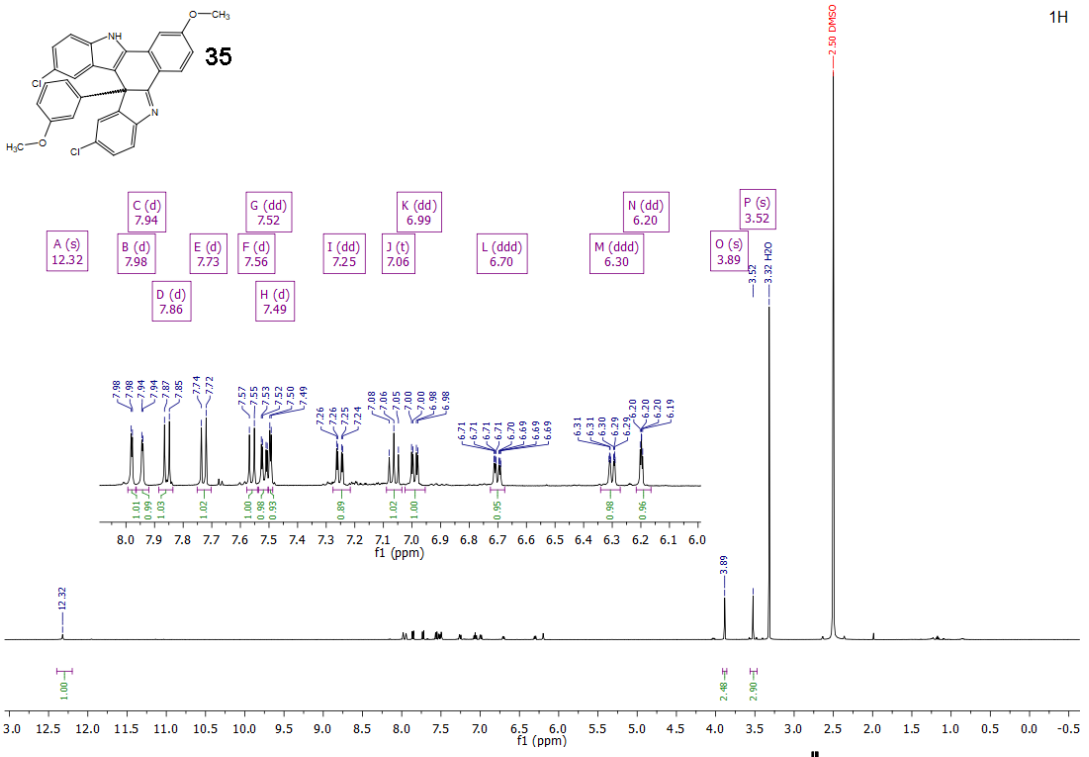

34
1H
A (s) 11.89
B (m) 8.07
C (dd) 7.68
D (s) 7.55
E (m) 7.49
F (td) 7.41
G (td) 7.33
H (ddd) 7.18
J (d) 6.65
K (m) 6.32
L (s) 3.92
M (s) 3.88
N (s) 3.57
O (s) 3.36
f1 (ppm)

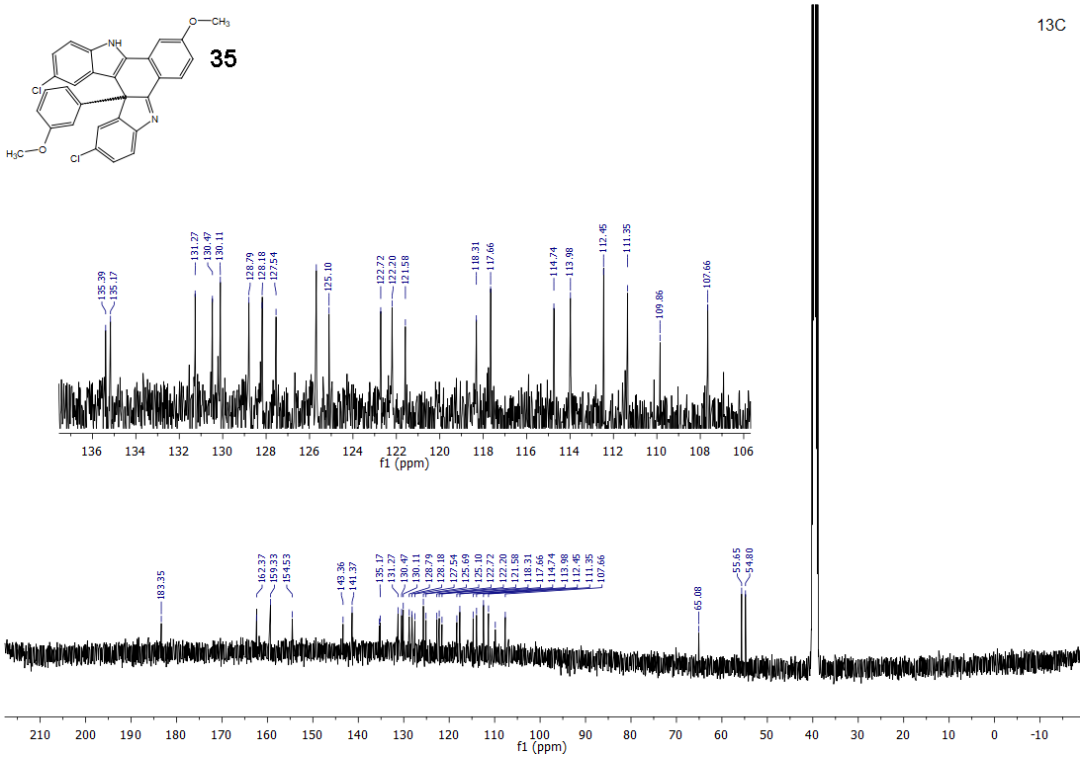

34
13C
39.52 DMSO-d6
55.86
55.78
55.35
55.22
f1 (ppm)

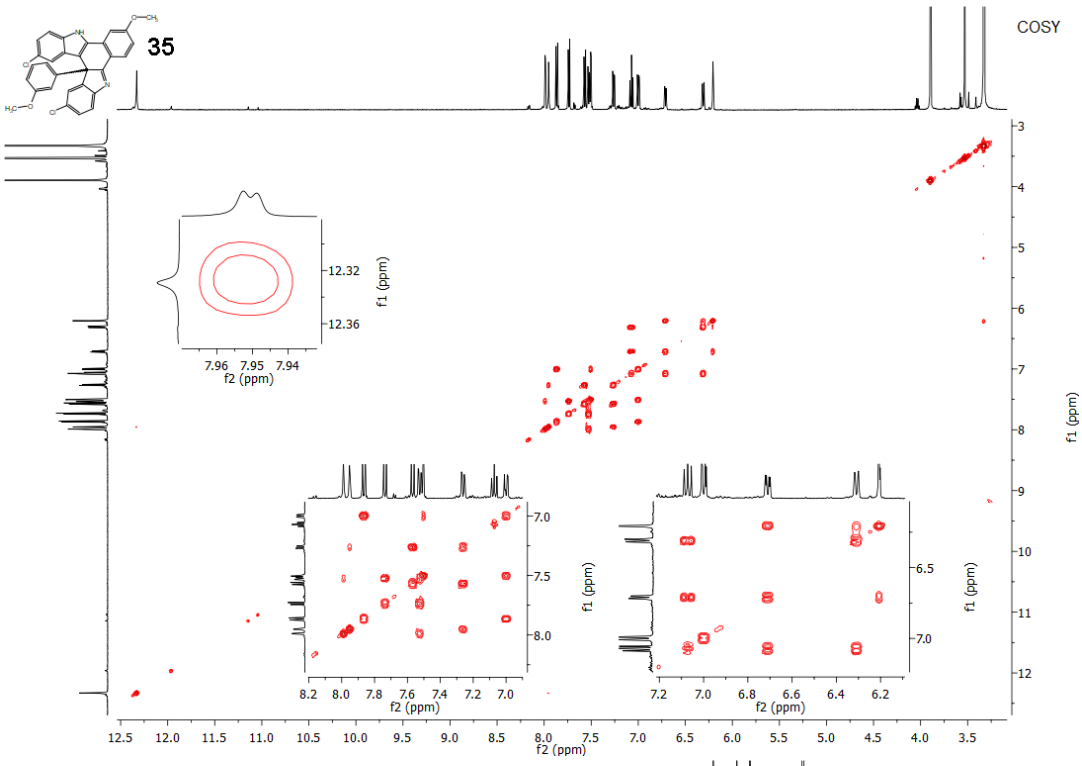

34
COSY
f1 (ppm)
f2 (ppm)

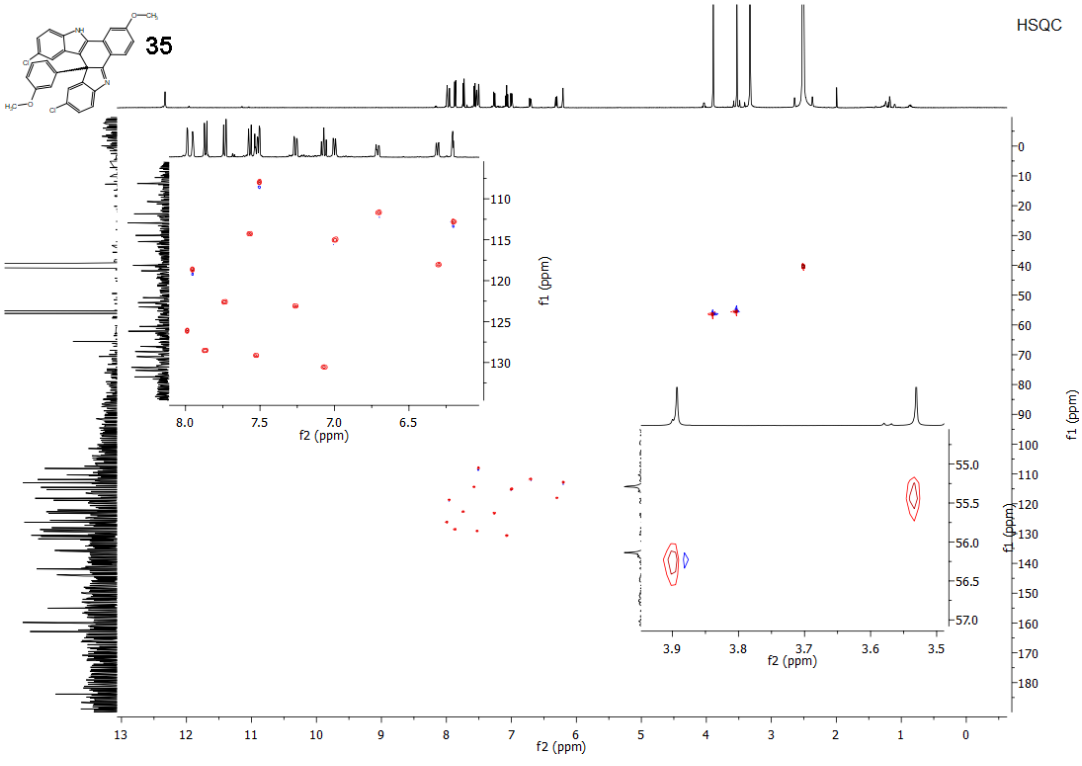

34
HSQC
f1 (ppm)
f2 (ppm)

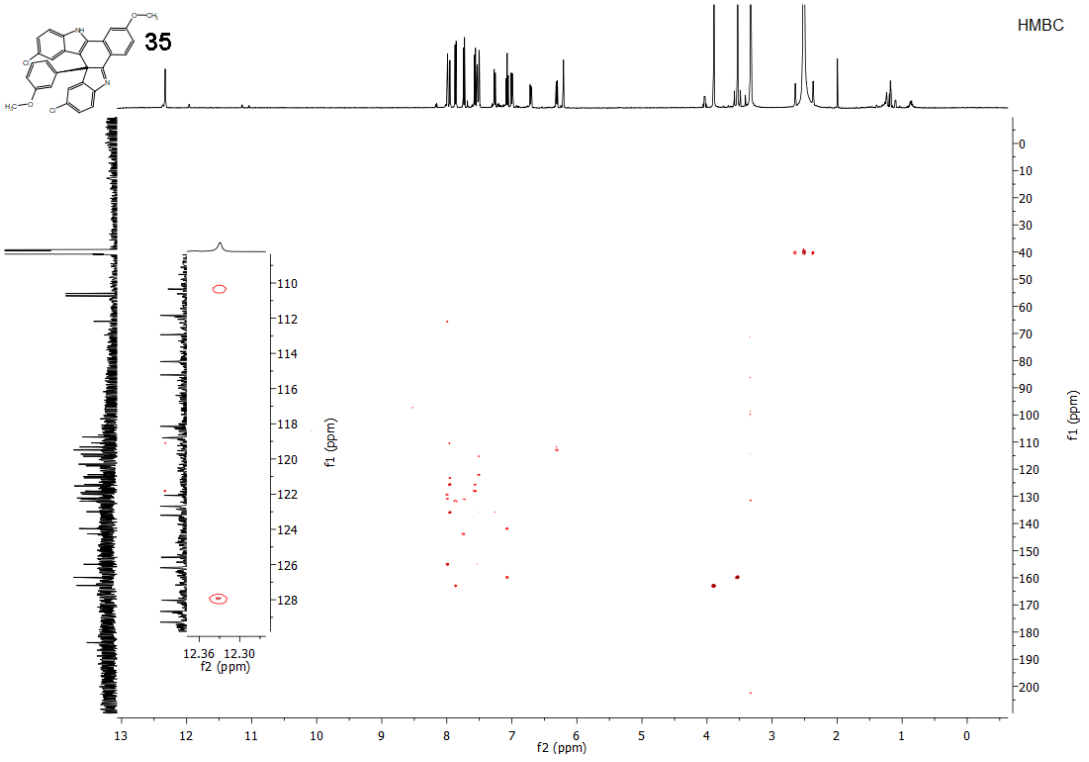

34
HMBC
f1 (ppm)
f2 (ppm)

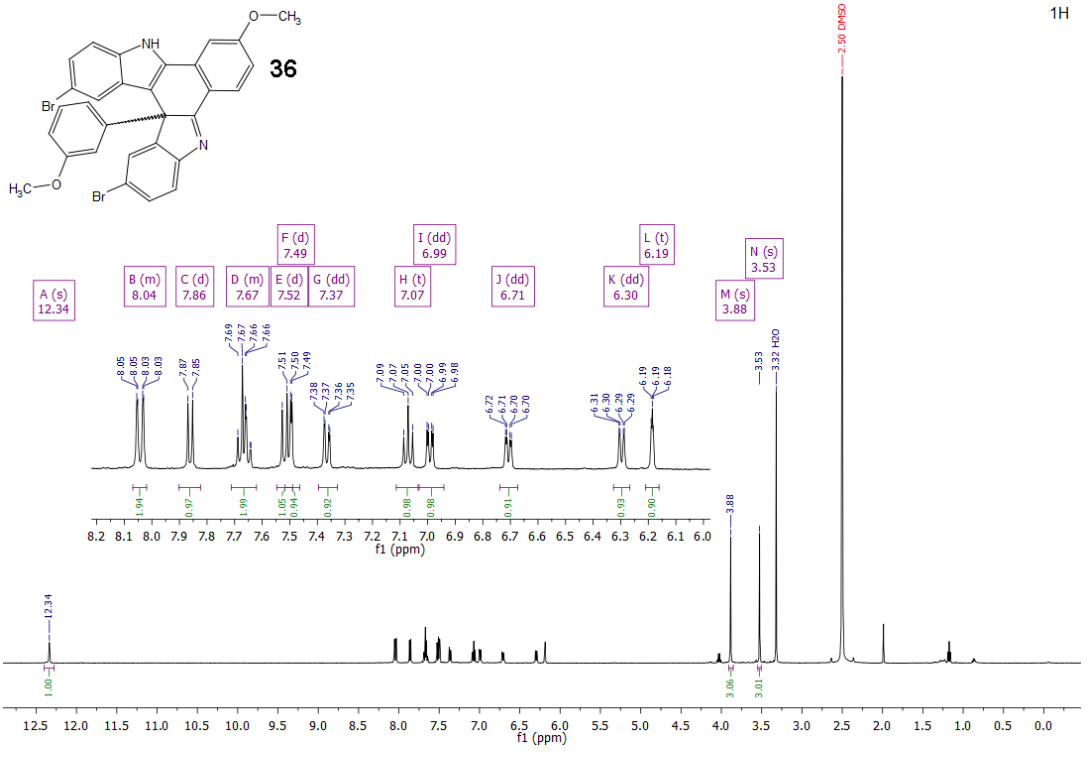

35
1H
A (s) 12.32
B (d) 7.98
C (d) 7.94
D (d) 7.86
E (d) 7.73
F (d) 7.56
G (dd) 7.52
H (d) 7.49
I (dd) 7.25
J (t) 7.06
K (dd) 6.99
L (ddd) 6.70
M (ddd) 6.30
N (dd) 6.20
O (s) 3.89
P (s) 3.52
2.50 DMSO
3.32 H2O
f1 (ppm)

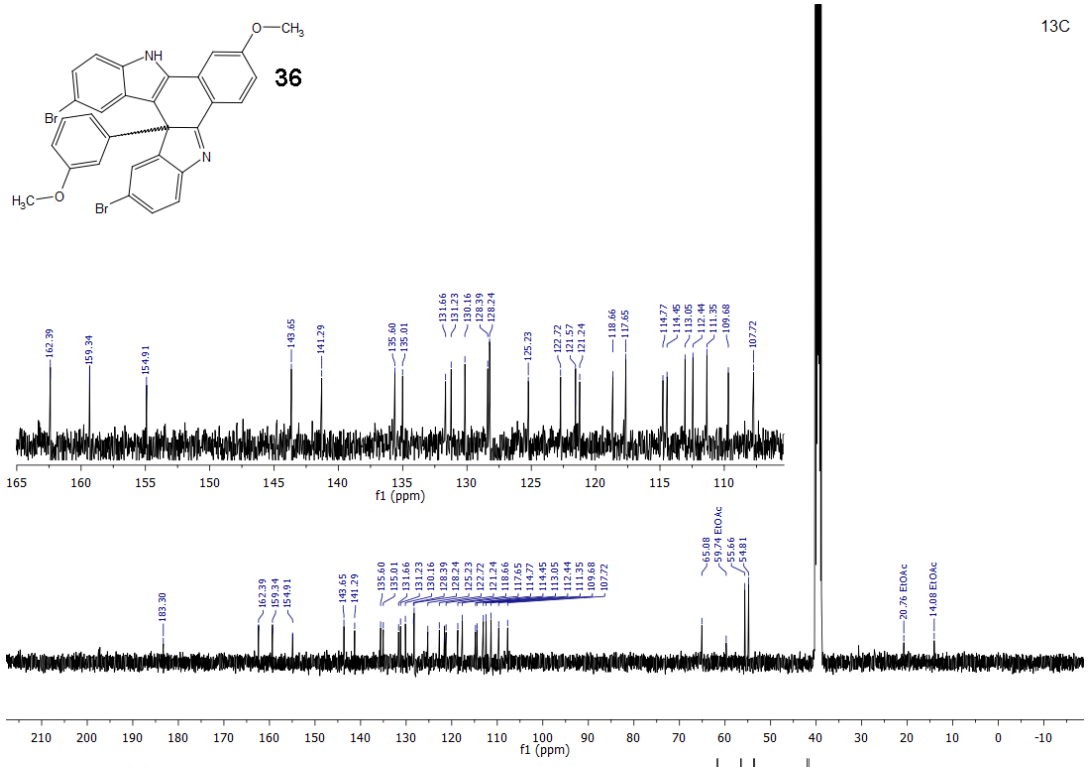

35
13C
f1 (ppm)

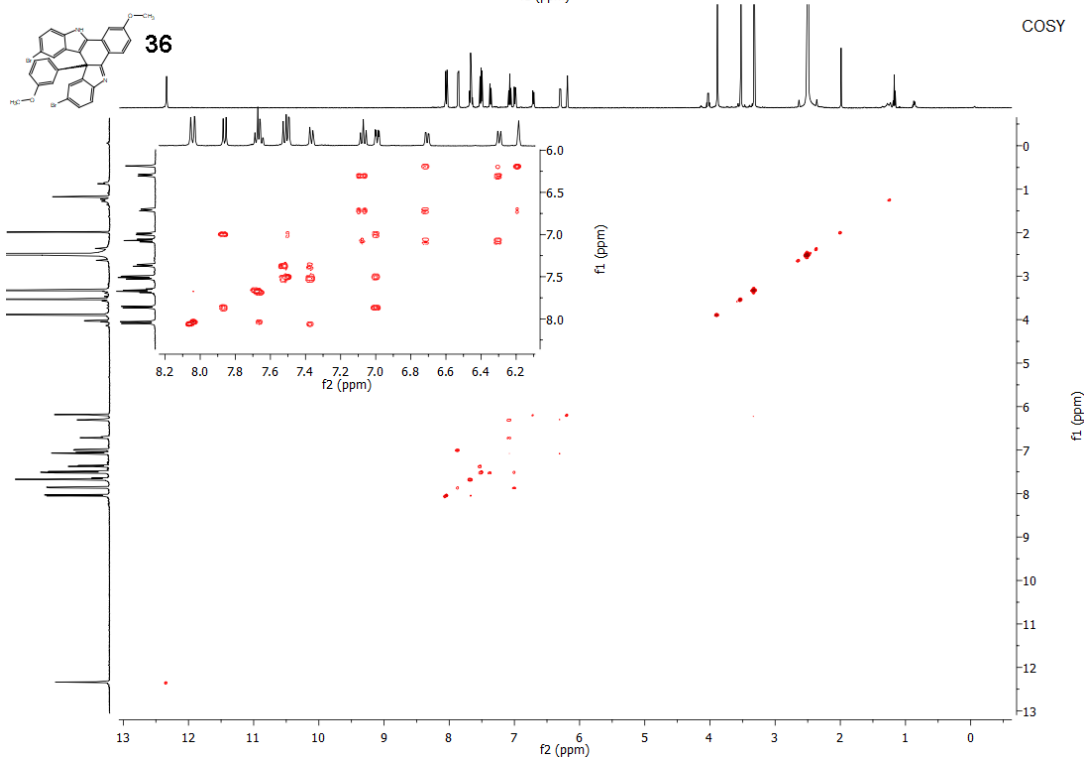

35
COSY
f1 (ppm)
f2 (ppm)

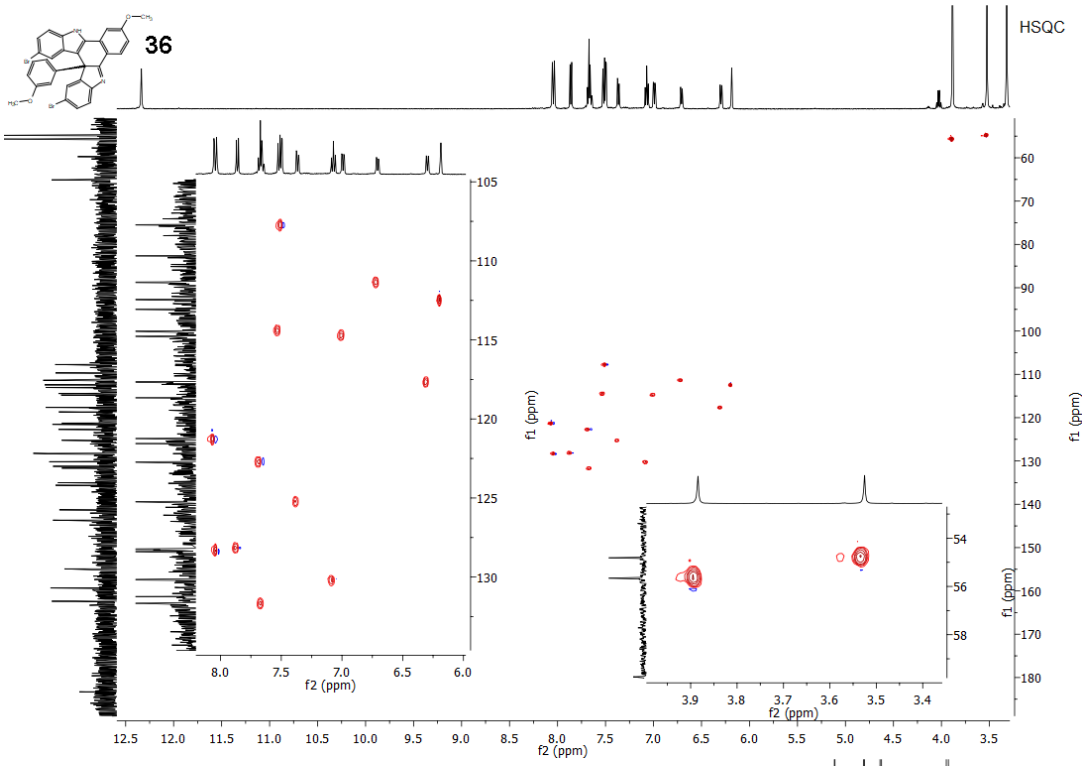

35
HSQC
f1 (ppm)
f2 (ppm)

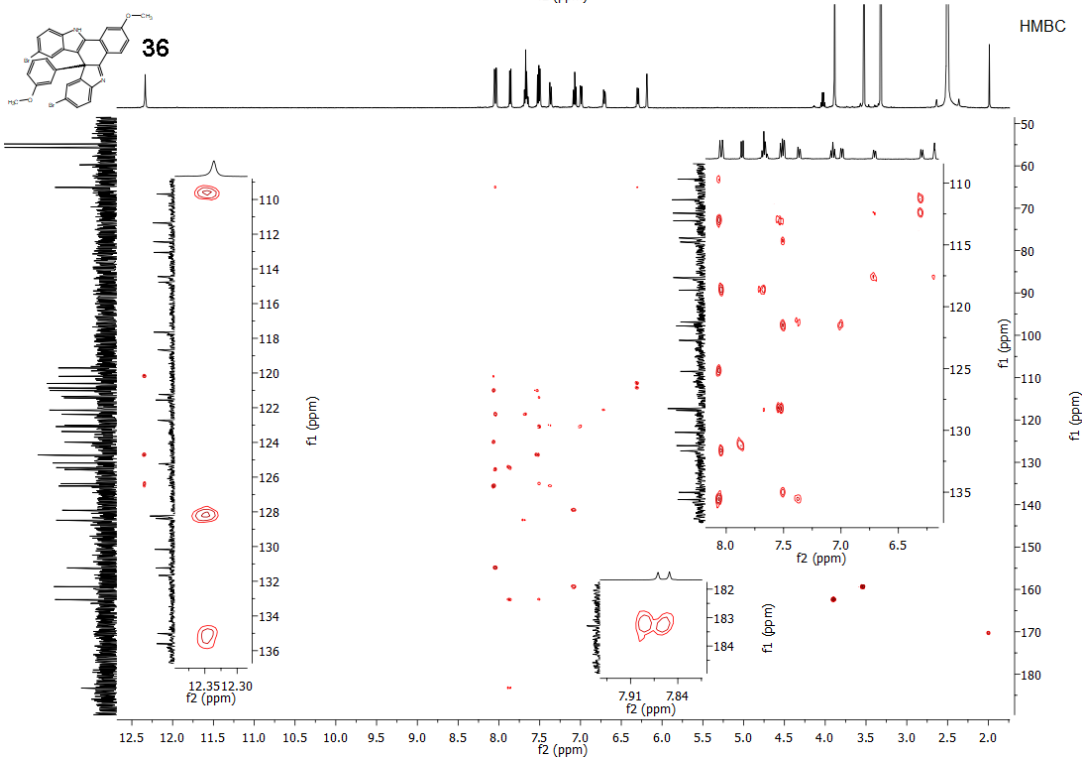

35
HMBC
f1 (ppm)
f2 (ppm)
12.36 12.30
f2 (ppm)

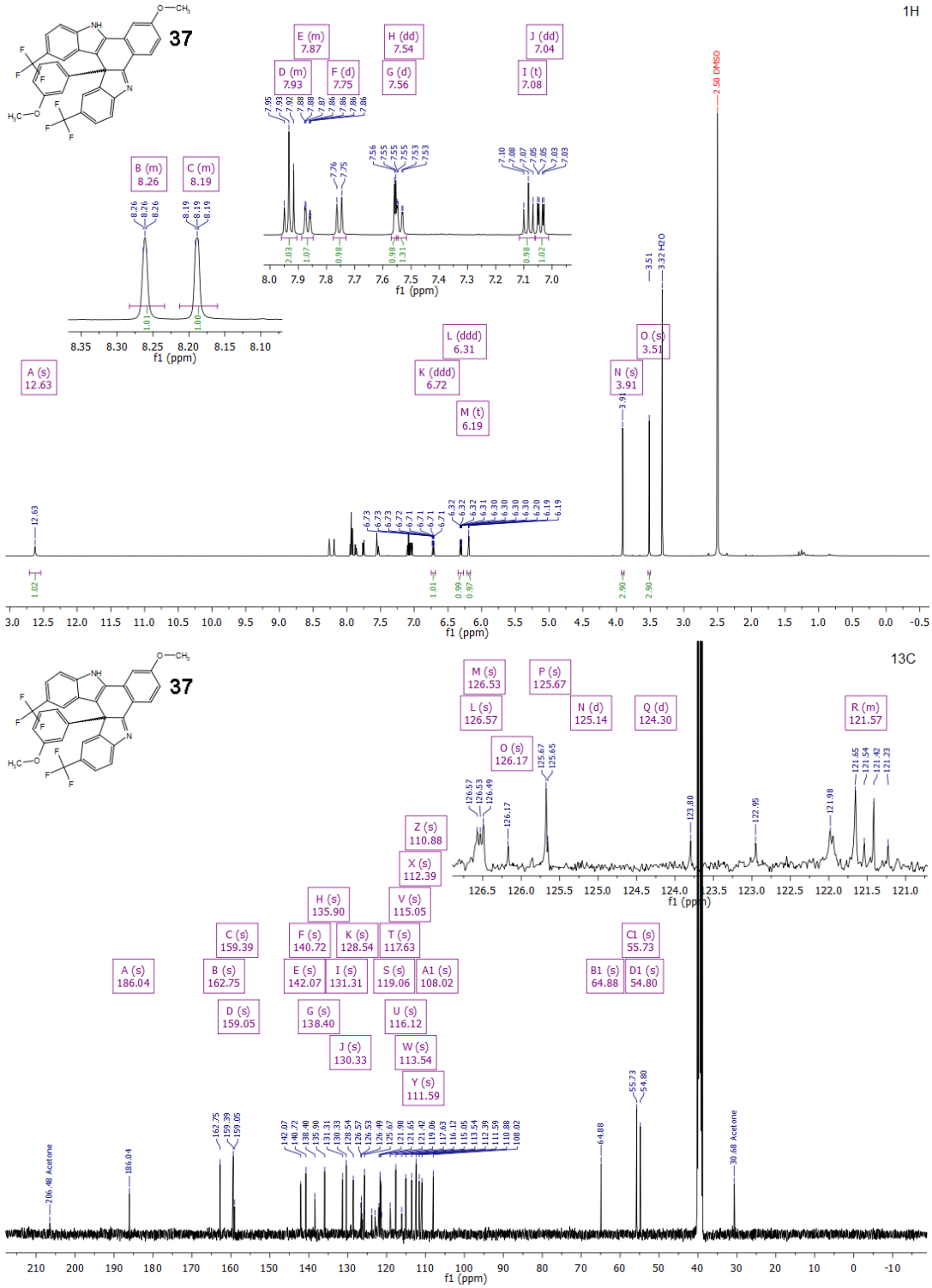

36
1H
A (s) 12.34
B (m) 8.04
C (d) 7.86
D (m) 7.67
E (d) 7.52
F (d) 7.49
G (dd) 7.37
H (t) 7.07
I (dd) 6.99
J (dd) 6.71
K (dd) 6.30
L (t) 6.19
M (s) 3.88
N (s) 3.53
2.50 DMSO
3.32 H2O
f1 (ppm)

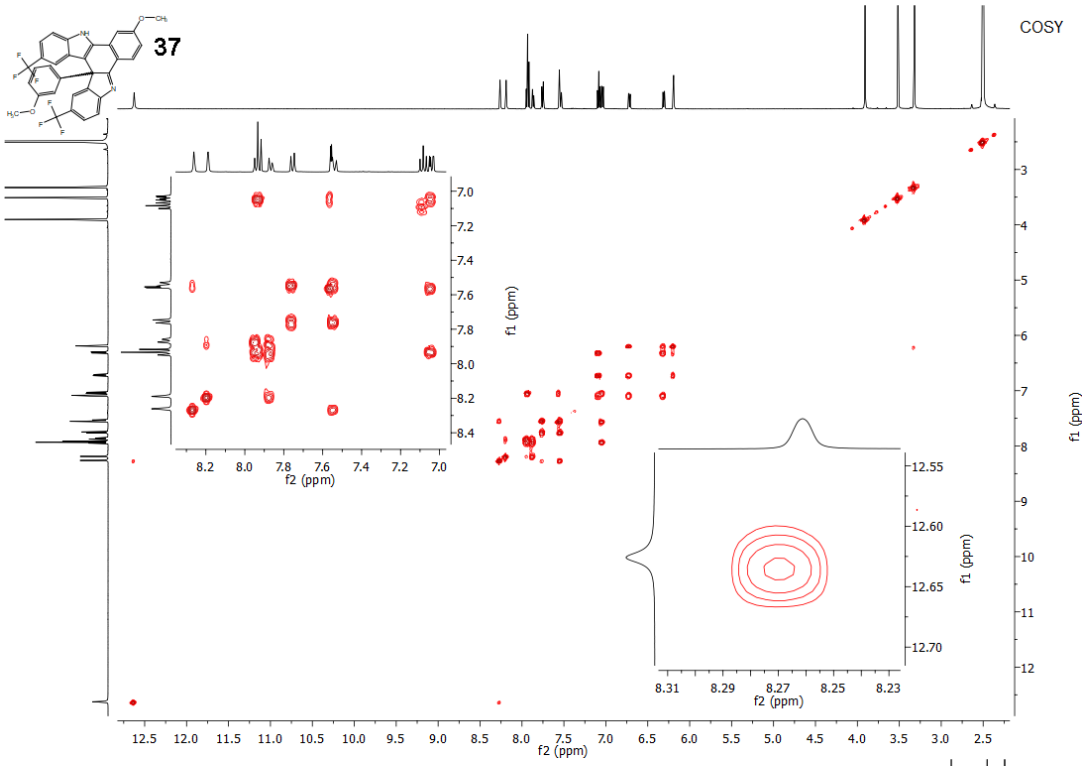

36
13C
f1 (ppm)

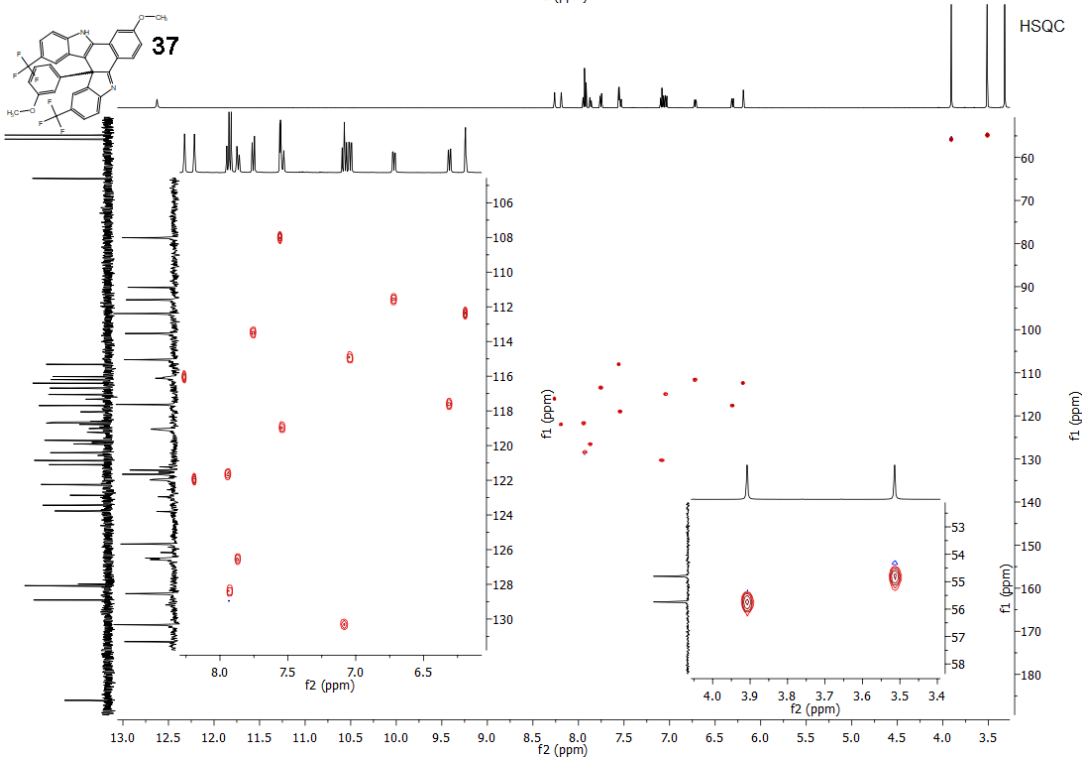

36
COSY
f1 (ppm)
f2 (ppm)

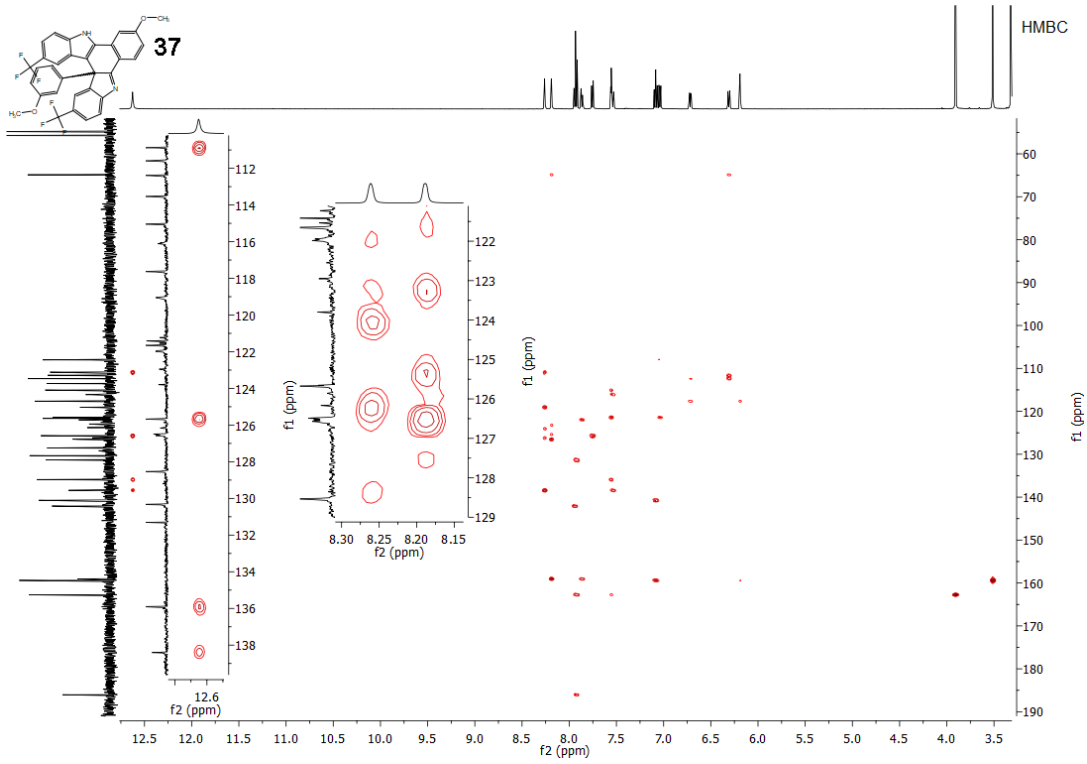

36
HSQC
f2 (ppm)
f1 (ppm)

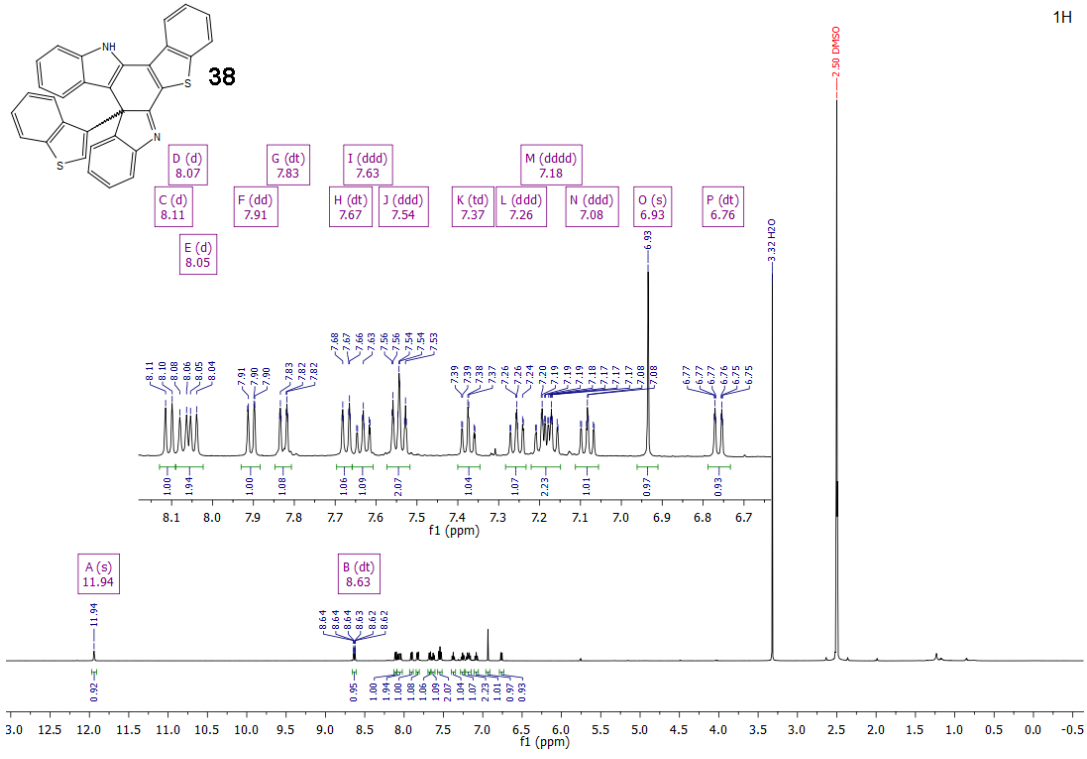

36
HMBC
f2 (ppm)
f1 (ppm)

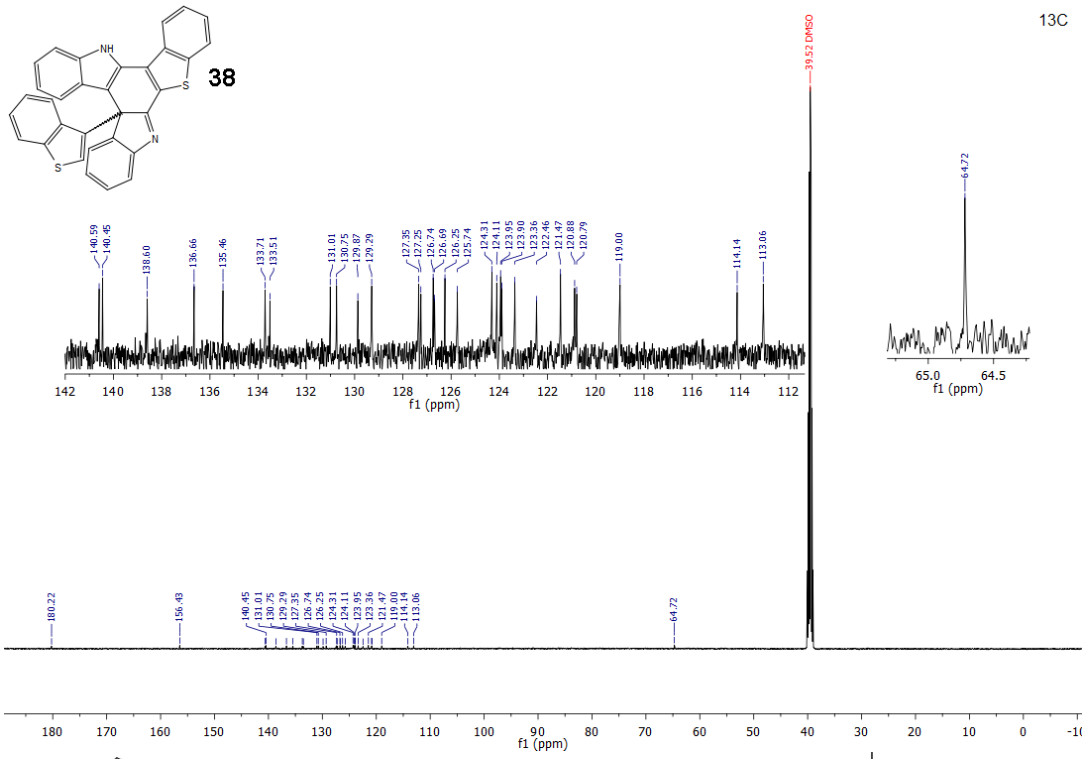

1H
37
A (s) 12.63
B (m) 8.26
C (m) 8.19
D (m) 7.93
E (m) 7.87
F (d) 7.75
G (d) 7.56
H (dd) 7.54
I (t) 7.08
J (dd) 7.04
K (ddd) 6.72
L (ddd) 6.31
M (t) 6.19
N (s) 3.91
O (s) 3.51
2.50 DMSO
3.32 H2O
f1 (ppm)
13C
37
A (s) 186.04
B (s) 162.75
C (s) 159.39
D (s) 159.05
E (s) 142.07
F (s) 140.72
G (s) 138.40
H (s) 135.90
I (s) 131.31
J (s) 130.33
K (s) 128.54
S (s) 119.06
T (s) 117.63
U (s) 116.12
V (s) 115.05
W (s) 113.54
X (s) 112.39
Y (s) 111.59
Z (s) 110.88
A1 (s) 108.02
B1 (s) 64.88
C1 (s) 55.73
D1 (s) 54.80
L (s) 126.57
M (s) 126.53
N (d) 125.14
O (s) 126.17
P (s) 125.67
Q (d) 124.30
R (m) 121.57
206.48 Acetone
30.68 Acetone
f1 (ppm)

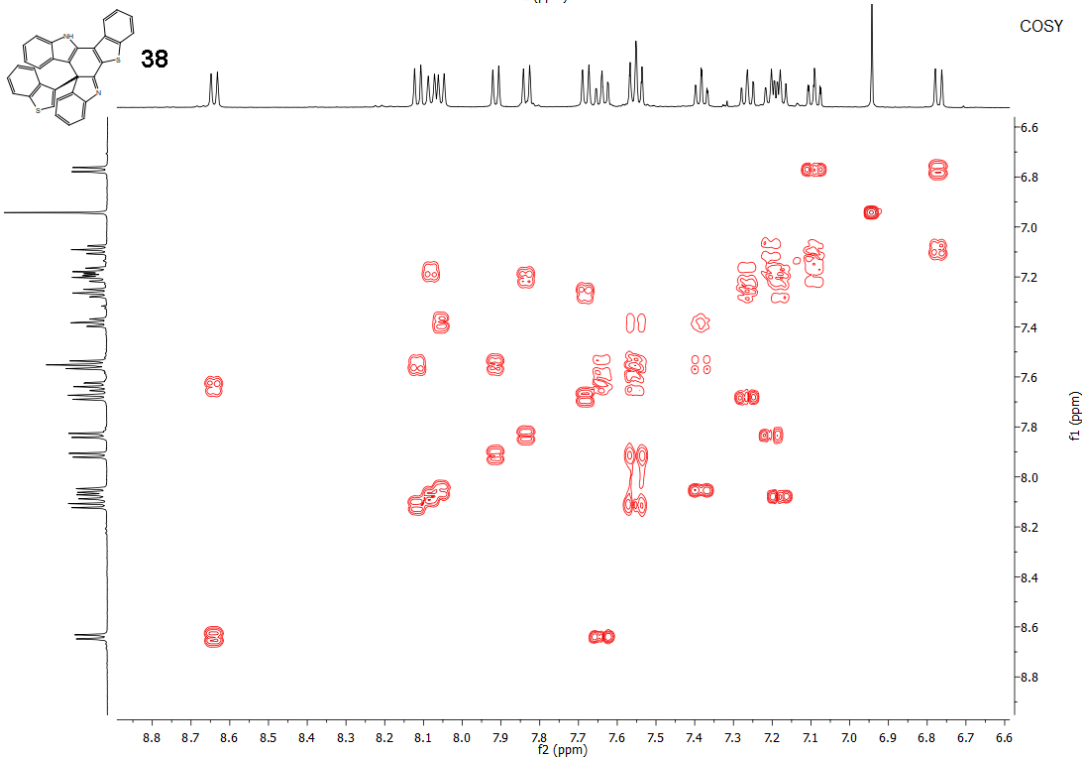

37
COSY
f1 (ppm)
f2 (ppm)

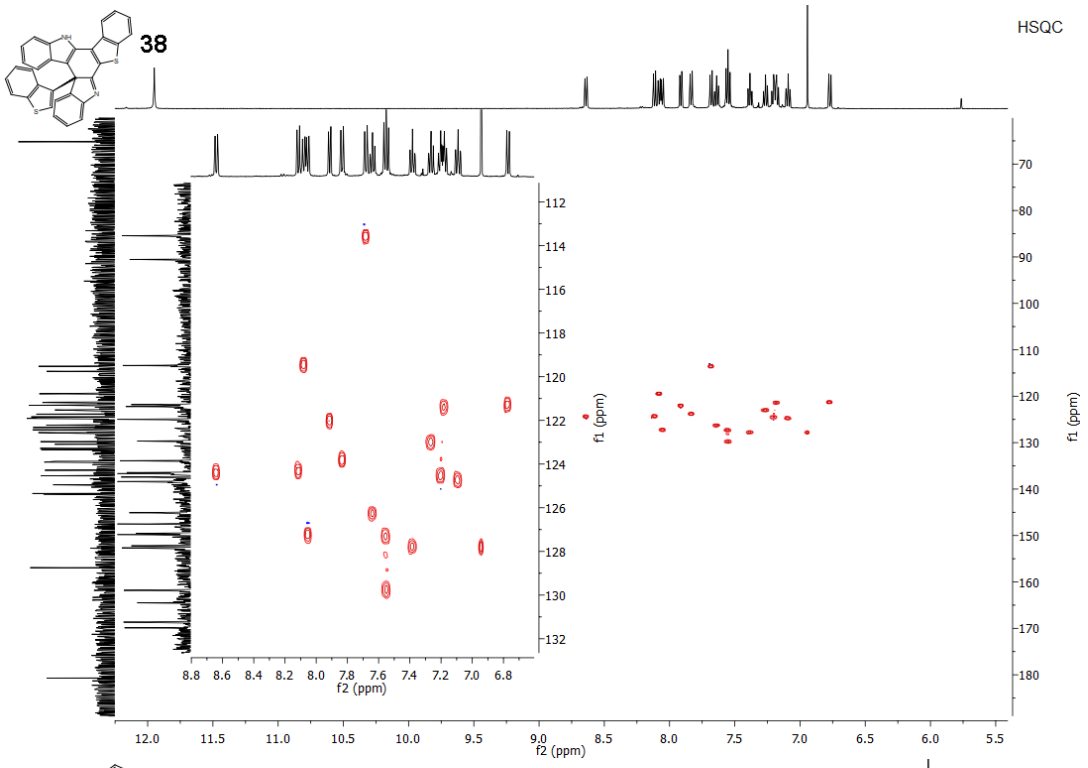

37
HSQC
f1 (ppm)
f2 (ppm)

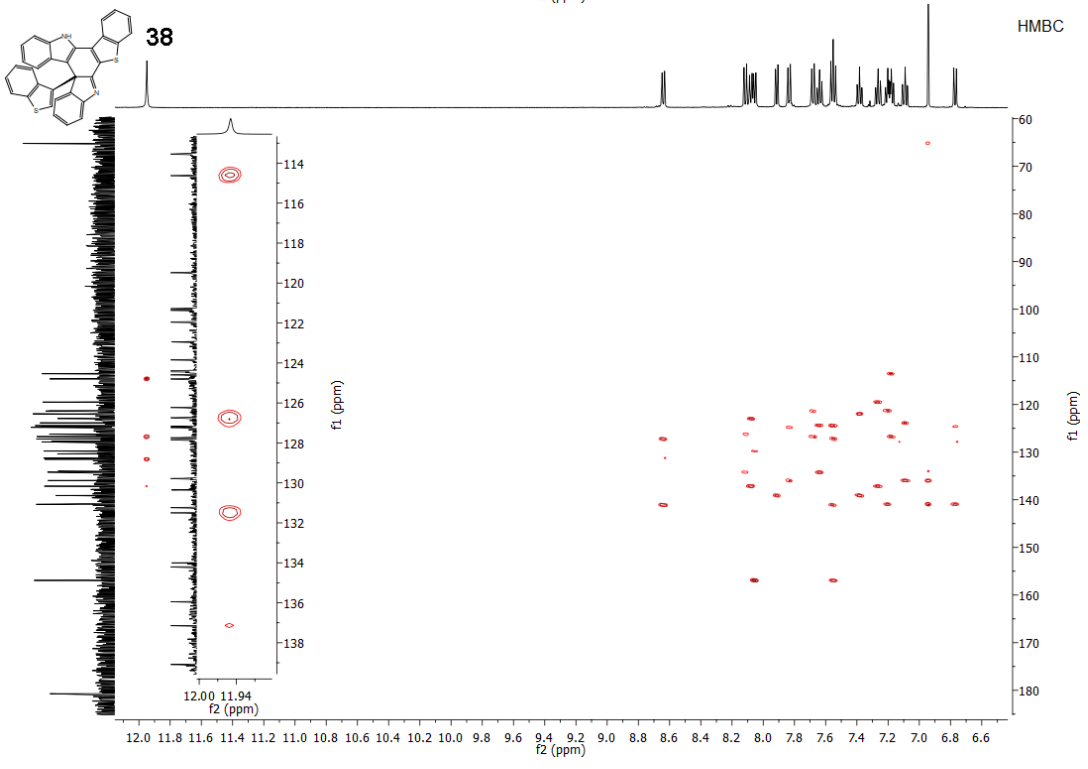

37
HMBC
f1 (ppm)
f2 (ppm)
12.6
8.30 8.25 8.20 8.15

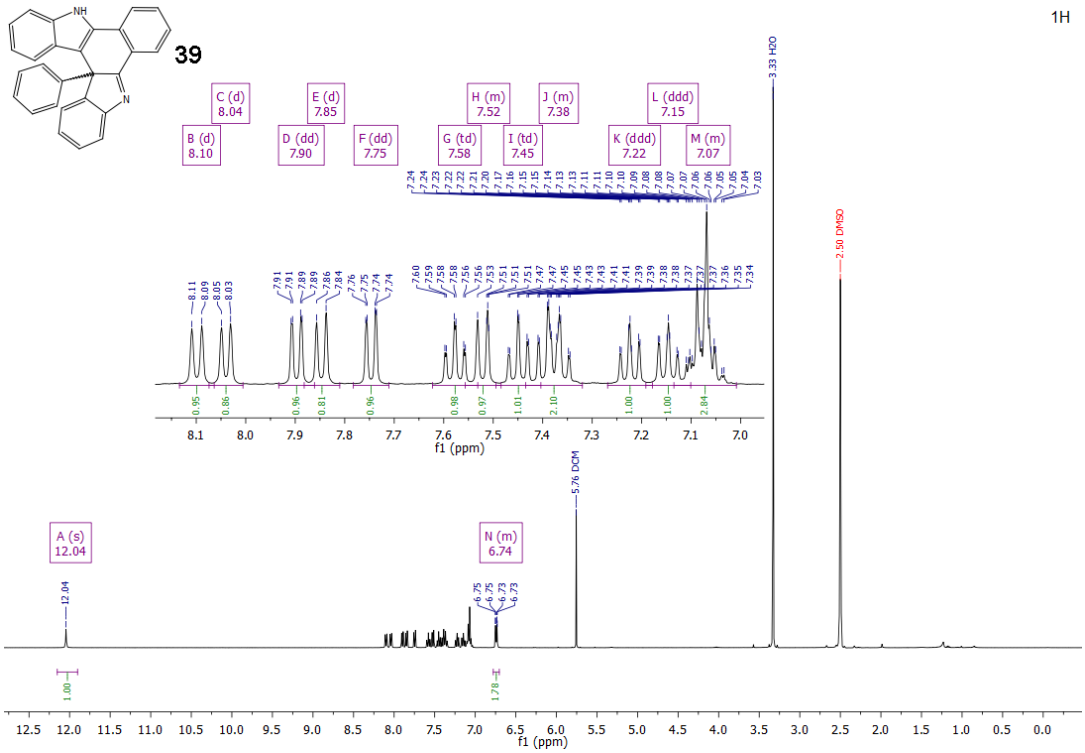

38
1H
D (d) 8.07
C (d) 8.11
E (d) 8.05
G (dt) 7.83
F (dd) 7.91
I (ddd) 7.63
H (dt) 7.67
J (ddd) 7.54
M (dddd) 7.18
K (td) 7.37
L (ddd) 7.26
N (ddd) 7.08
O (s) 6.93
P (dt) 6.76
A (s) 11.94
B (dt) 8.63
2.50 DMSO
3.32 H2O
f1 (ppm)

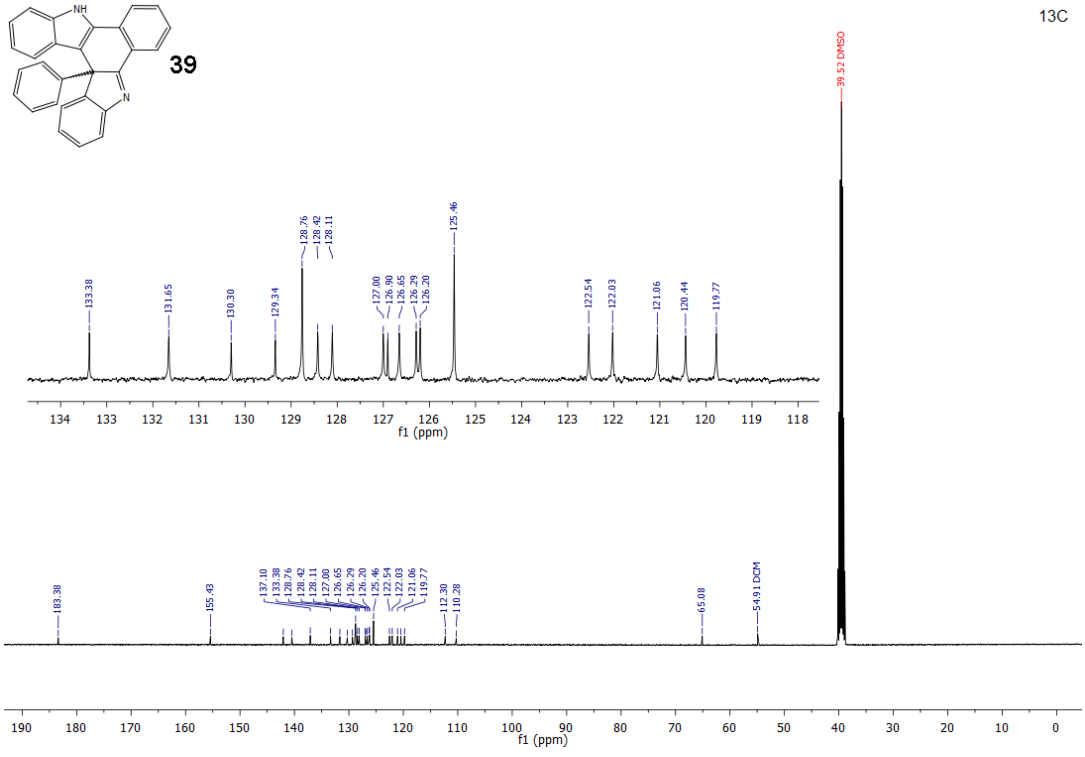

38
13C
39.52 DMSO
64.72
140.59
140.45
138.60
136.66
135.46
133.71
133.51
131.01
130.75
129.87
129.29
127.35
127.25
126.74
126.69
126.25
125.74
124.31
124.11
123.95
123.90
123.36
122.46
121.47
120.88
120.79
119.00
114.14
113.06
180.22
156.48
f1 (ppm)

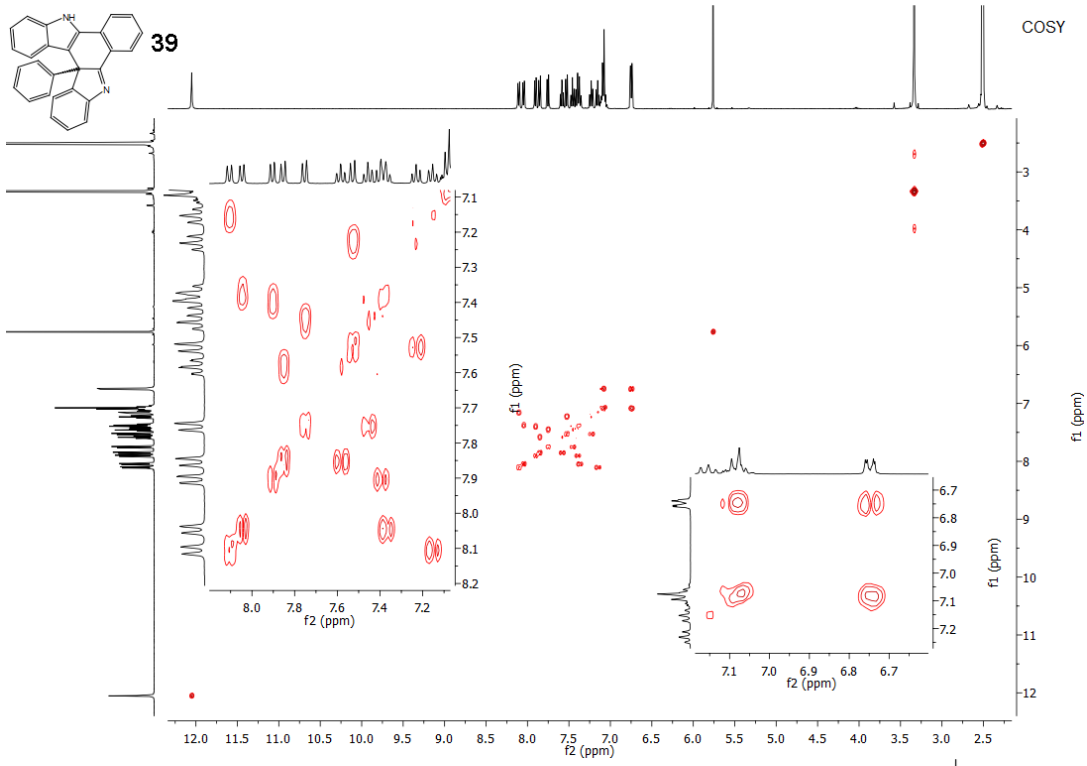

38
COSY
f2 (ppm)
f1 (ppm)

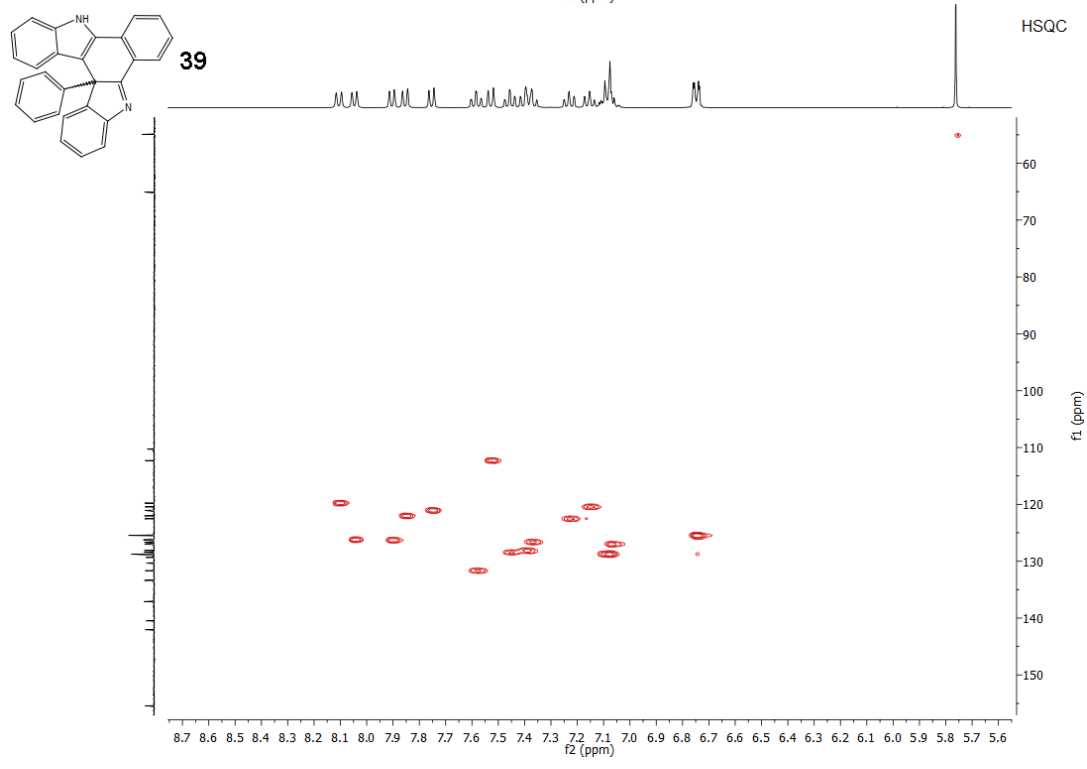

38
HSQC
f2 (ppm)
f1 (ppm)

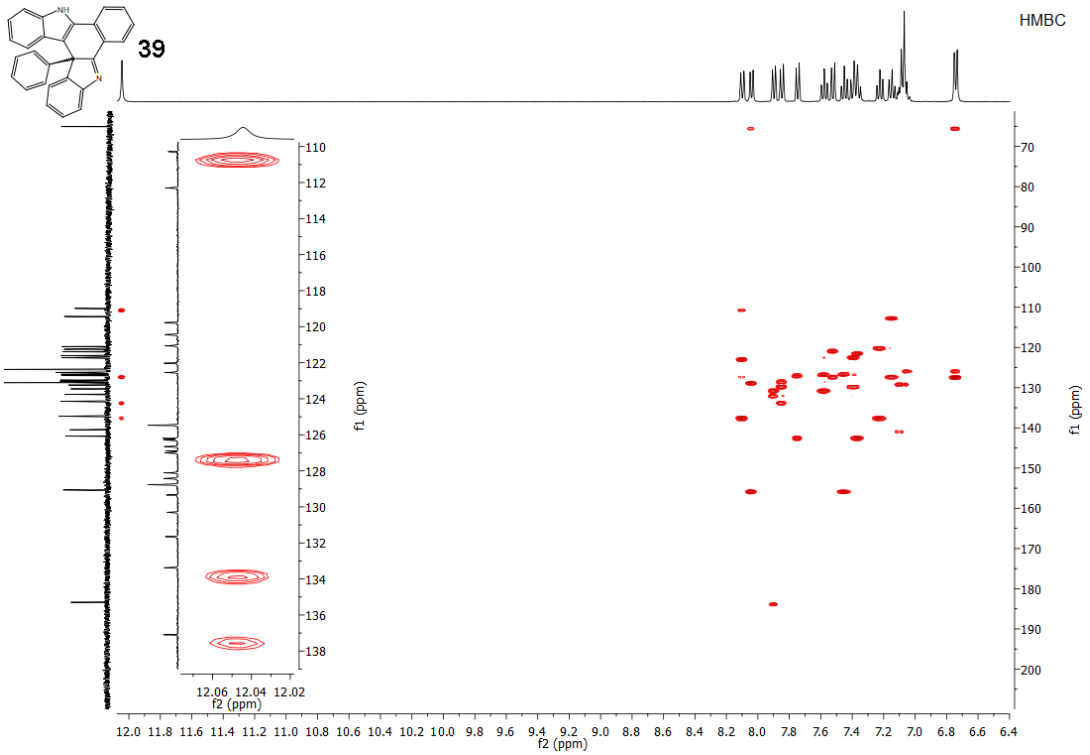

38
HMBC
f2 (ppm)
f1 (ppm)

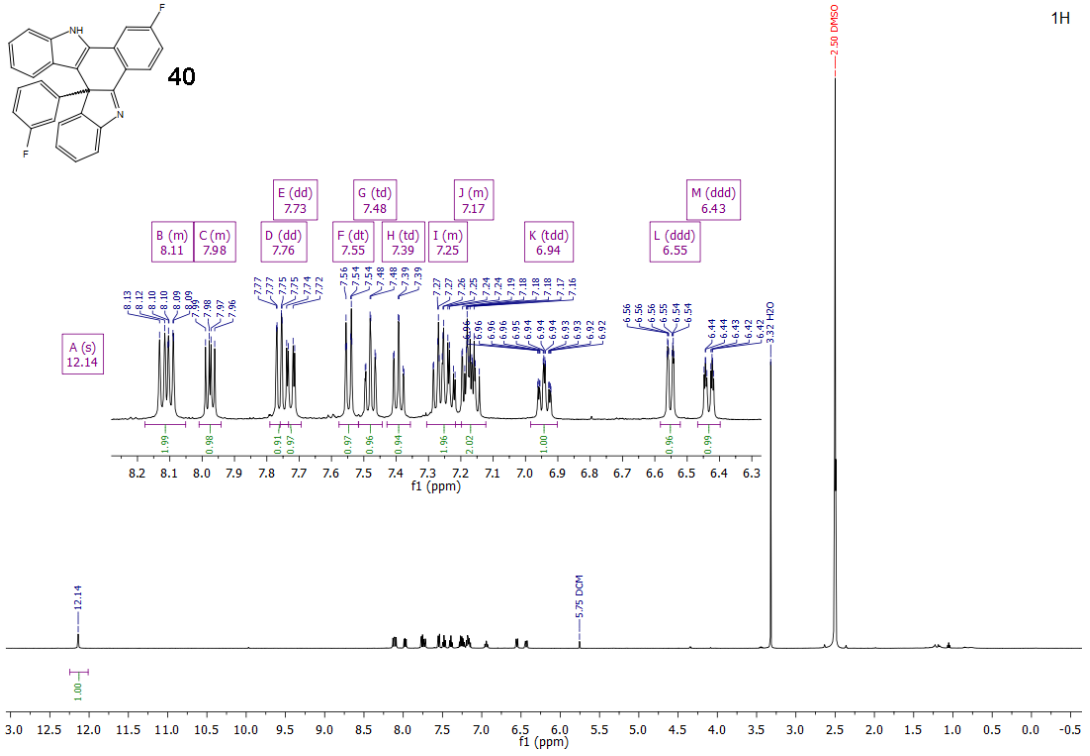

1H
39
A (s) 12.04
B (d) 8.10
C (d) 8.04
D (dd) 7.90
E (d) 7.85
F (dd) 7.75
G (td) 7.58
H (m) 7.52
I (td) 7.45
J (m) 7.38
K (ddd) 7.22
L (ddd) 7.15
M (m) 7.07
N (m) 6.74
3.33 H2O
2.50 DMSO
5.76 DCM
f1 (ppm)

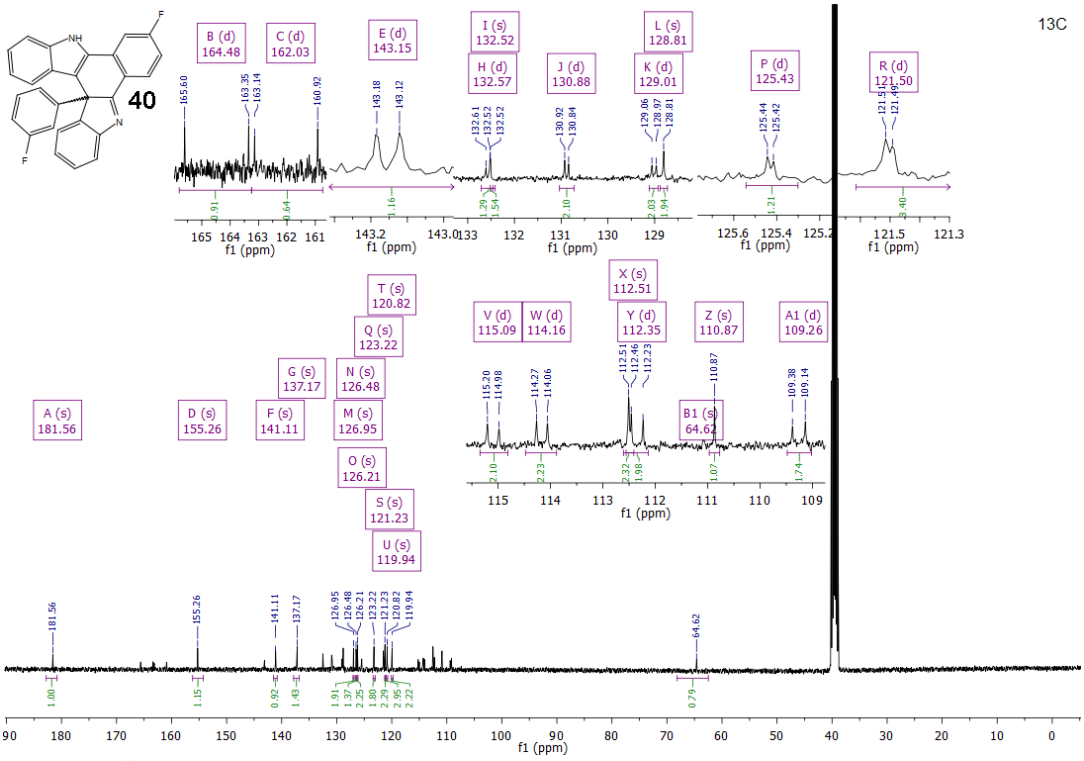

13C
39
39.52 DMSO
54.91 DCM
f1 (ppm)

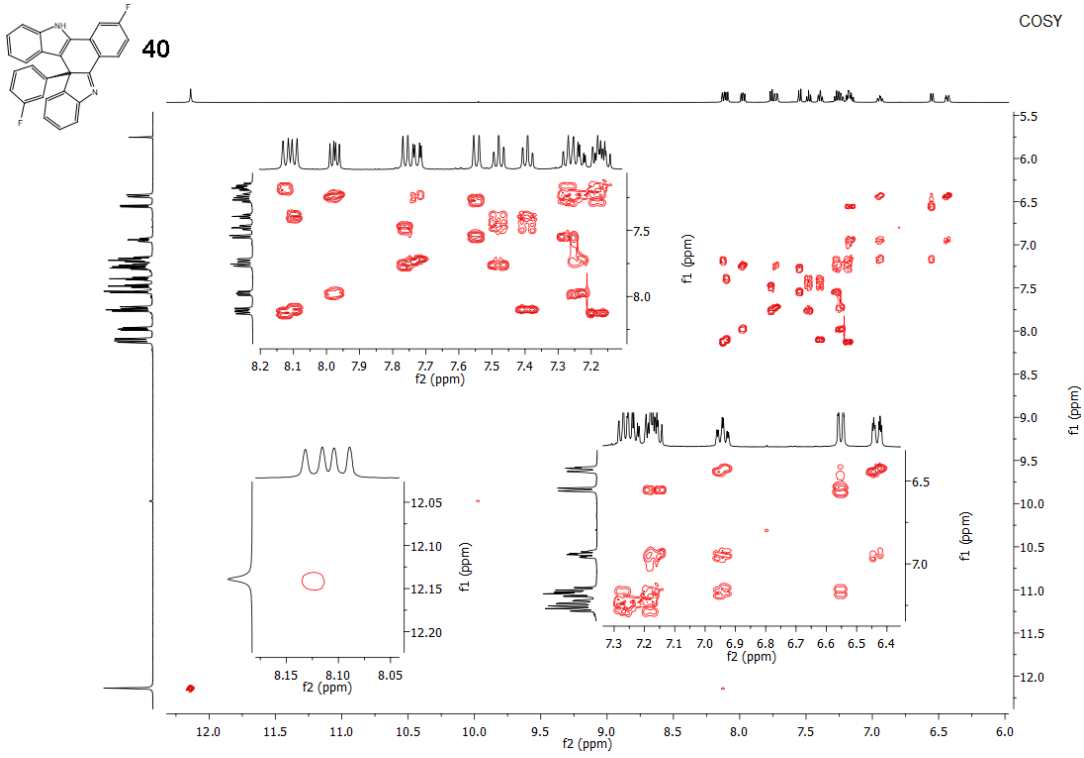

39
COSY
f1 (ppm)
f2 (ppm)

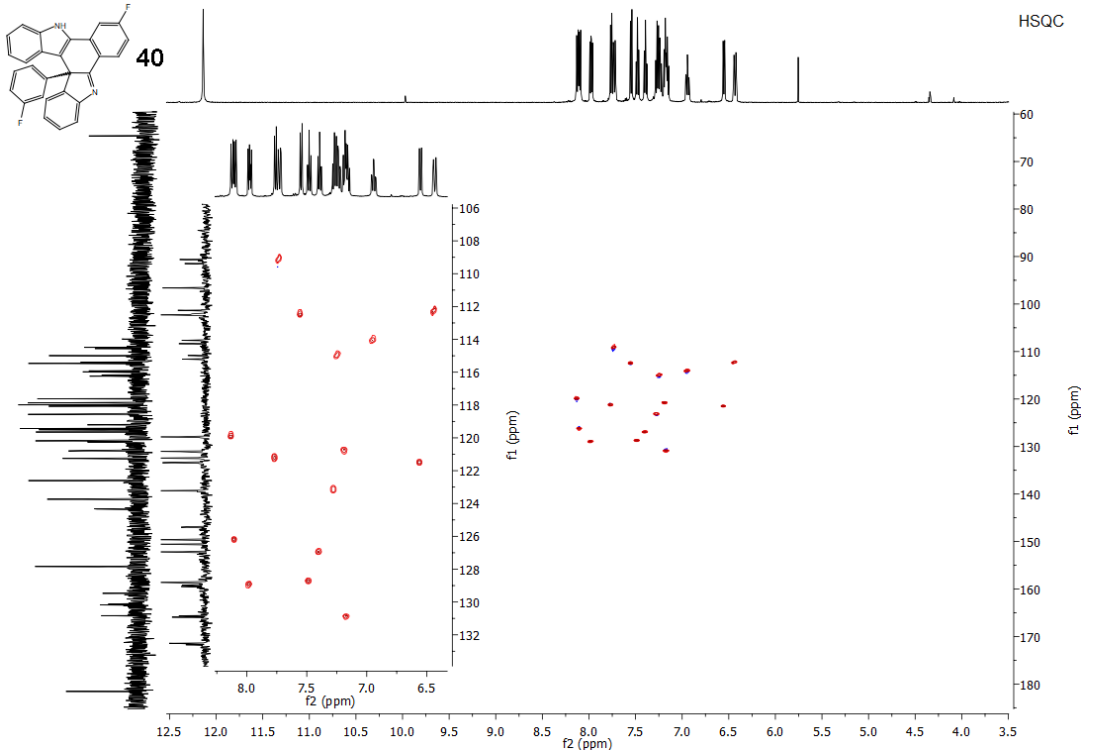

39
HSQC
f1 (ppm)
f2 (ppm)

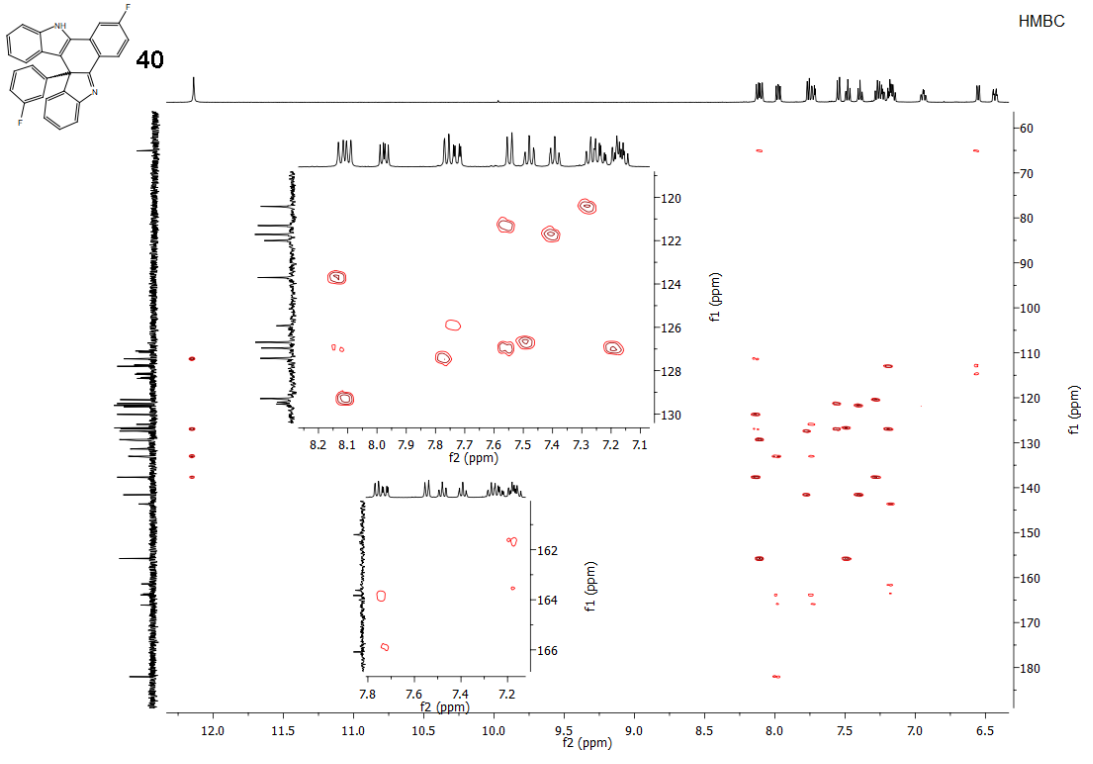

39
HMBC
f1 (ppm)
f2 (ppm)

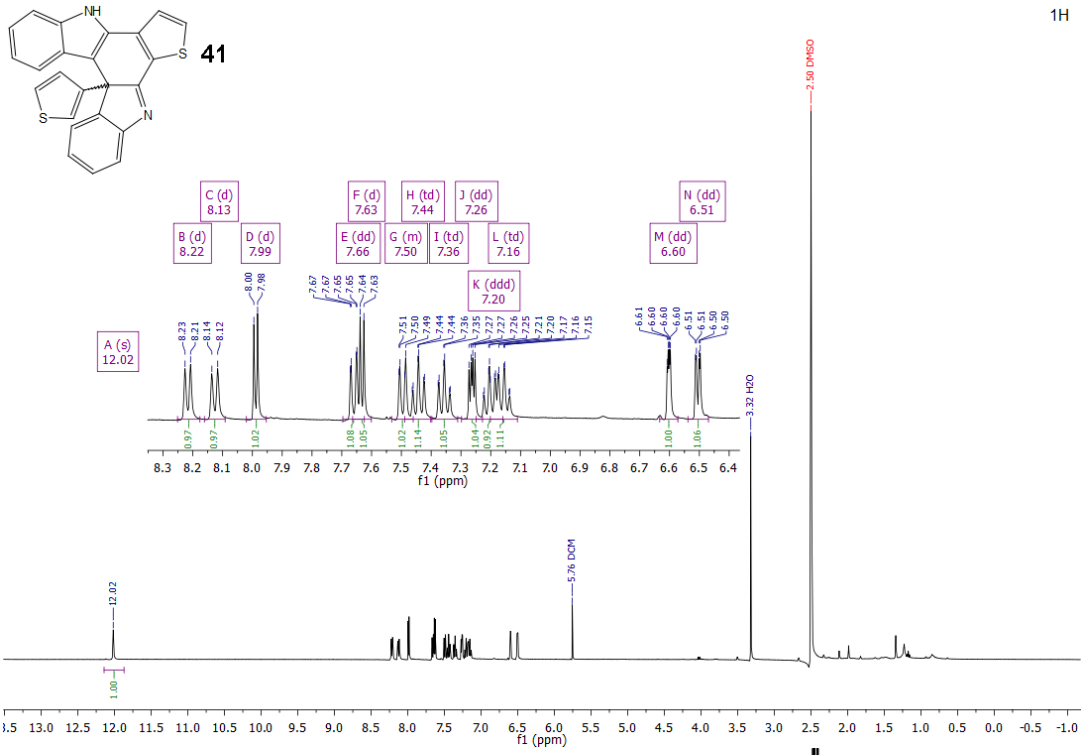

40
1H
B (m) 8.11
C (m) 7.98
D (dd) 7.76
E (dd) 7.73
F (dt) 7.55
G (td) 7.48
H (td) 7.39
I (m) 7.25
J (m) 7.17
K (tdd) 6.94
L (ddd) 6.55
M (ddd) 6.43
A (s) 12.14
2.50 DMSO
3.32 H2O
5.75 DCM
f1 (ppm)

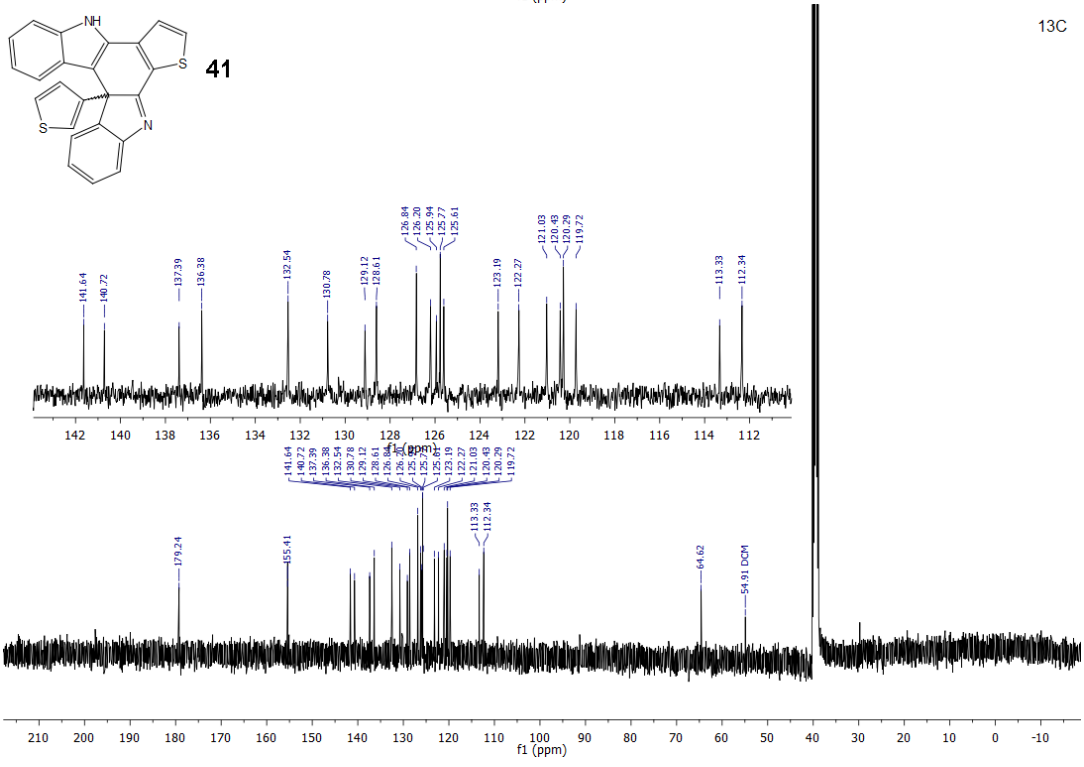

13C
40
B (d) 164.48
C (d) 162.03
E (d) 143.15
I (s) 132.52
H (d) 132.57
J (d) 130.88
L (s) 128.81
K (d) 129.01
P (d) 125.43
R (d) 121.50
T (s) 120.82
Q (s) 123.22
G (s) 137.17
N (s) 126.48
V (d) 115.09
W (d) 114.16
X (s) 112.51
Y (d) 112.35
Z (s) 110.87
A1 (d) 109.26
A (s) 181.56
D (s) 155.26
F (s) 141.11
M (s) 126.95
B1 (s) 64.62
O (s) 126.21
S (s) 121.23
U (s) 119.94
f1 (ppm)

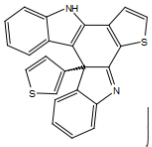

COSY
40
f1 (ppm)
f2 (ppm)


40
HSQC
f2 (ppm)
f1 (ppm)


40
HMBC
f2 (ppm)
f1 (ppm)

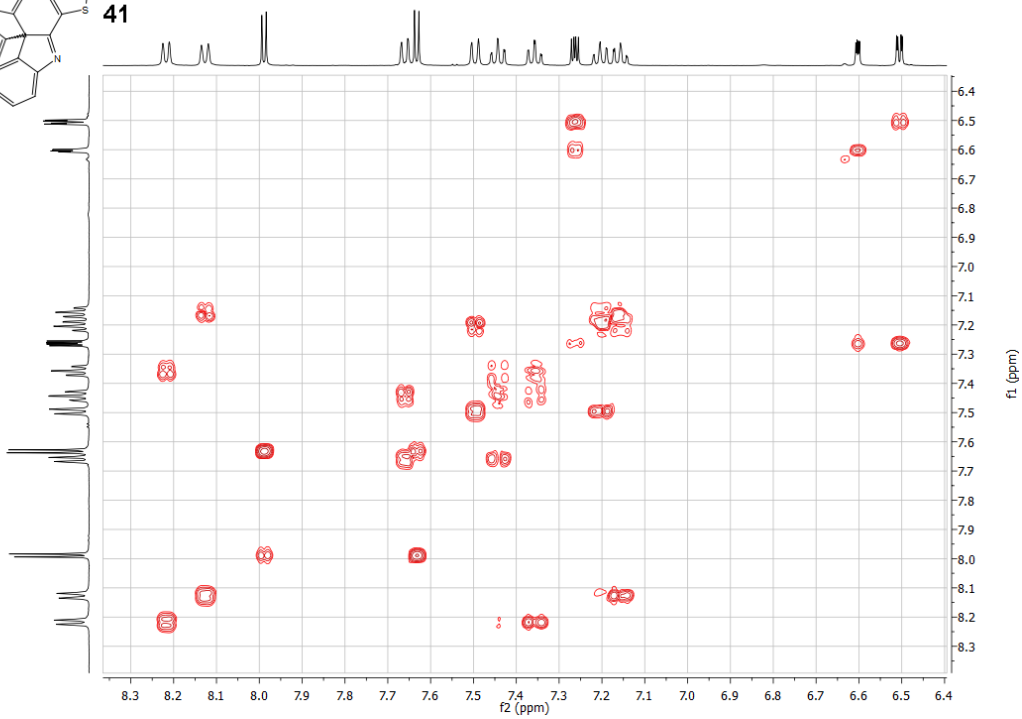

41
1H
A (s) 12.02
B (d) 8.22
C (d) 8.13
D (d) 7.99
E (dd) 7.66
F (d) 7.63
G (m) 7.50
H (td) 7.44
I (td) 7.36
J (dd) 7.26
K (ddd) 7.20
L (td) 7.16
M (dd) 6.60
N (dd) 6.51
2.50 DMSO
3.32 H2O
5.76 DCM
f1 (ppm)

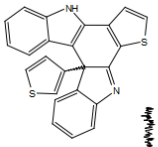

41
13C
141.64
140.72
137.39
136.38
132.54
130.78
129.12
128.61
126.84
126.20
125.94
125.77
125.61
123.19
122.27
121.03
120.43
120.29
119.72
113.33
112.34
179.24
155.41
64.62
54.91 DCM
f1 (ppm)



41

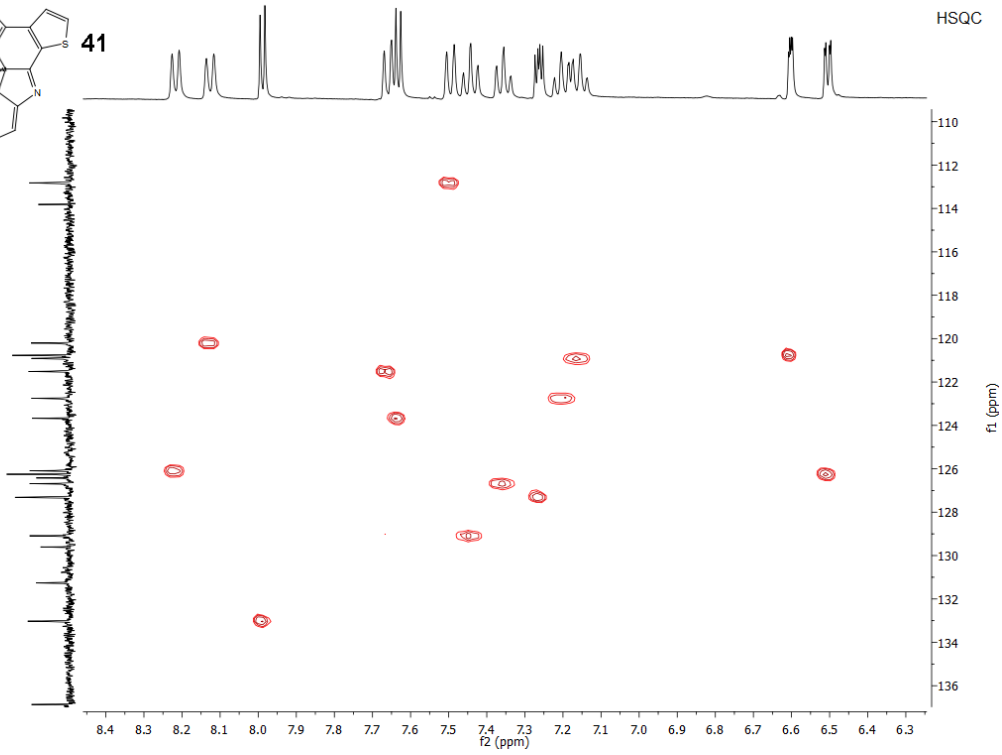
COSY

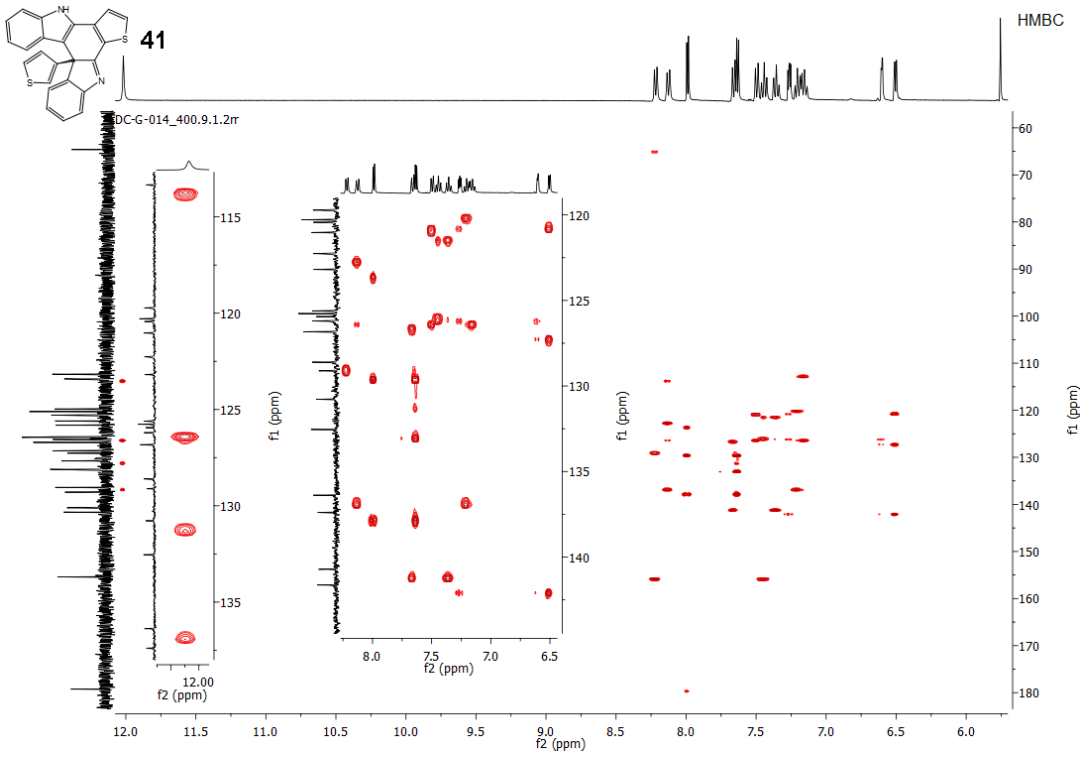


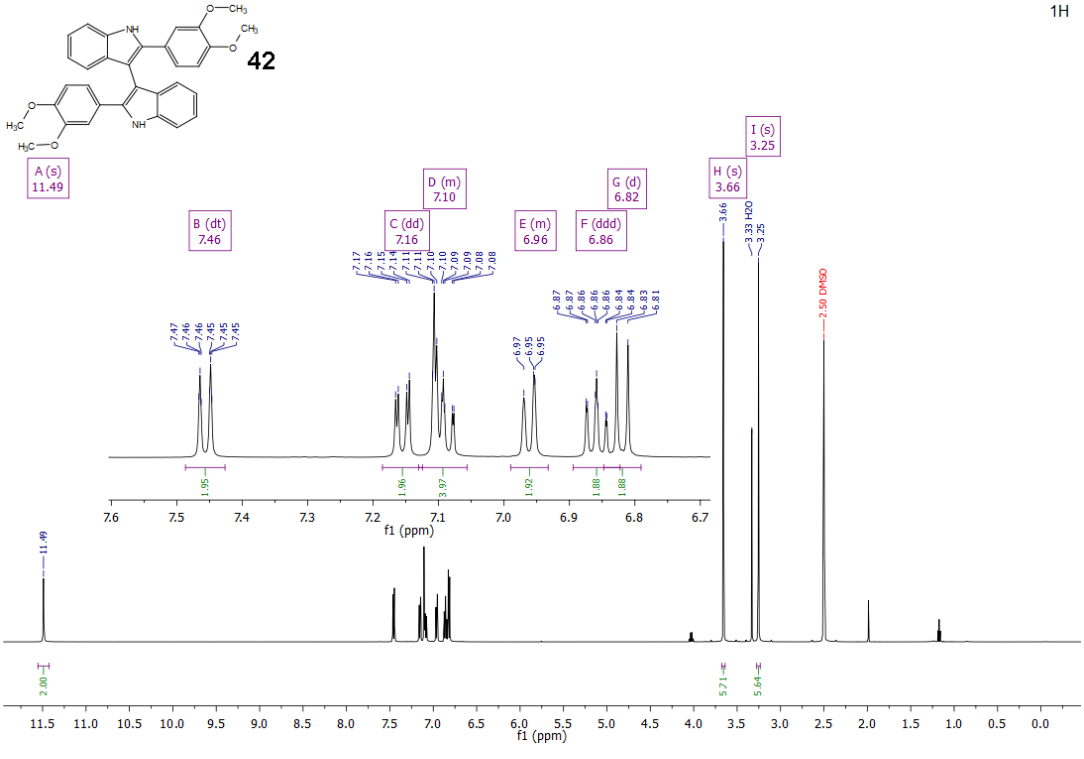


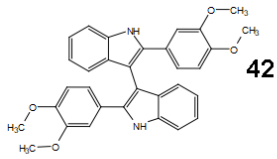
41

HSQC



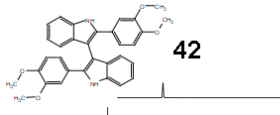

41
HMBC
DC-G-014_400.9.1.2rr
f1 (ppm)
f2 (ppm)
12.00


42
1H
A (s) 11.49
B (dt) 7.46
C (dd) 7.16
D (m) 7.10
E (m) 6.96
F (ddd) 6.86
G (d) 6.82
H (s) 3.66
I (s) 3.25
3.33 H2O
2.50 DMSO
f1 (ppm)



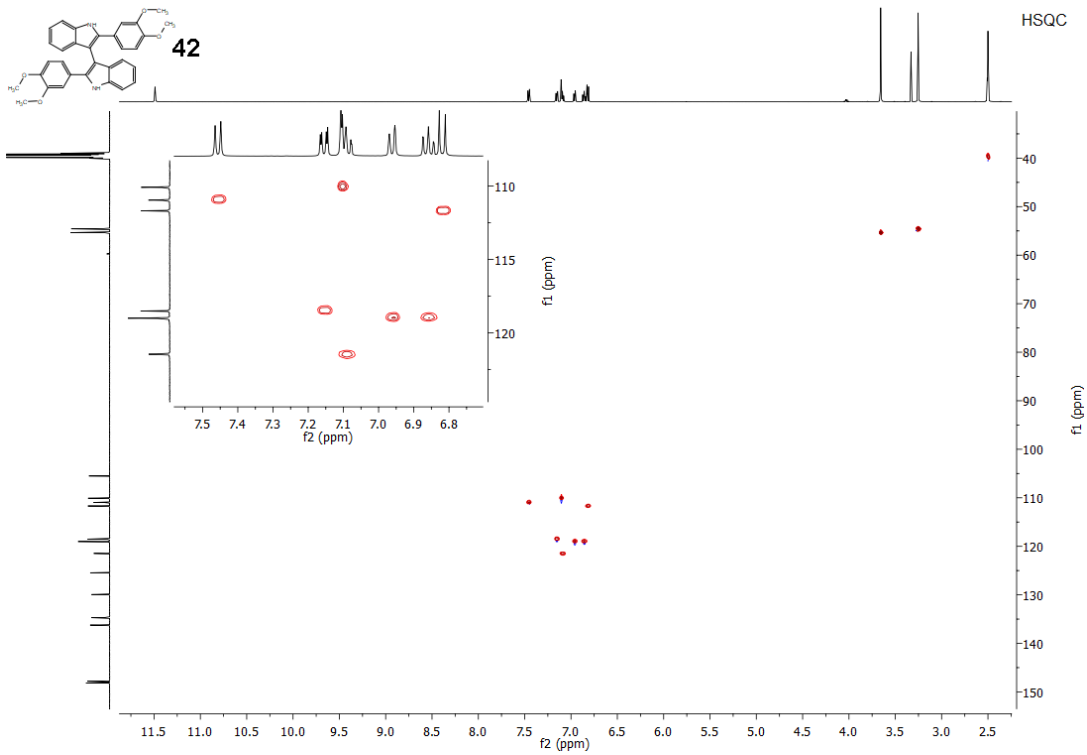
42

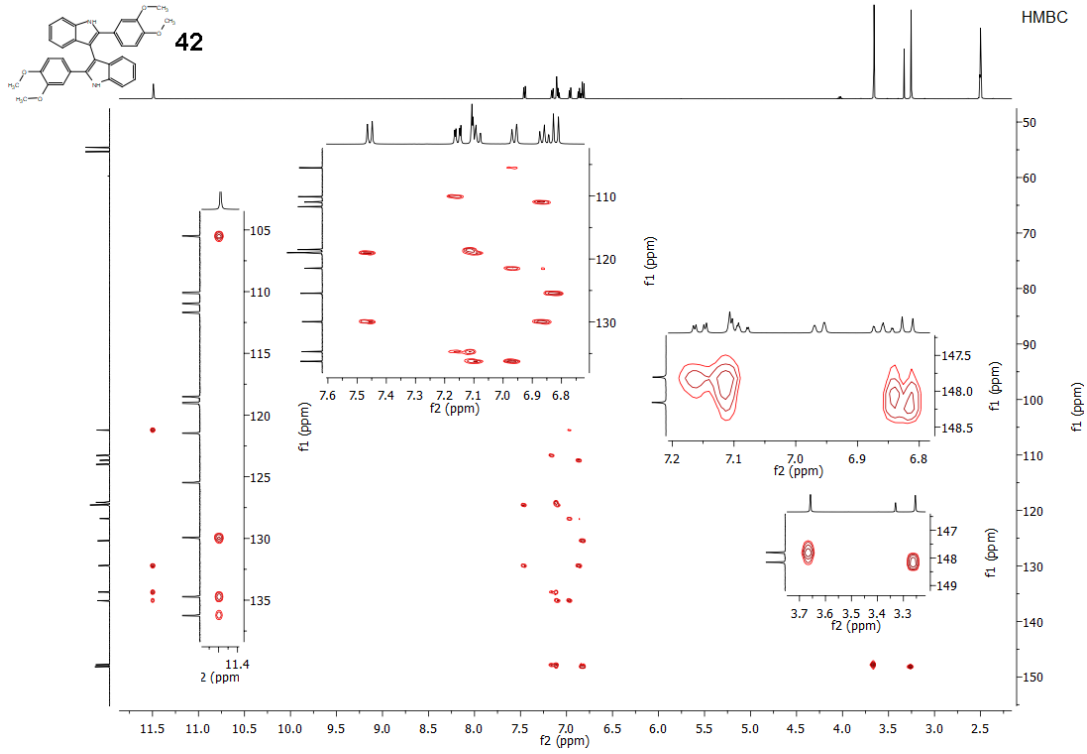
13C

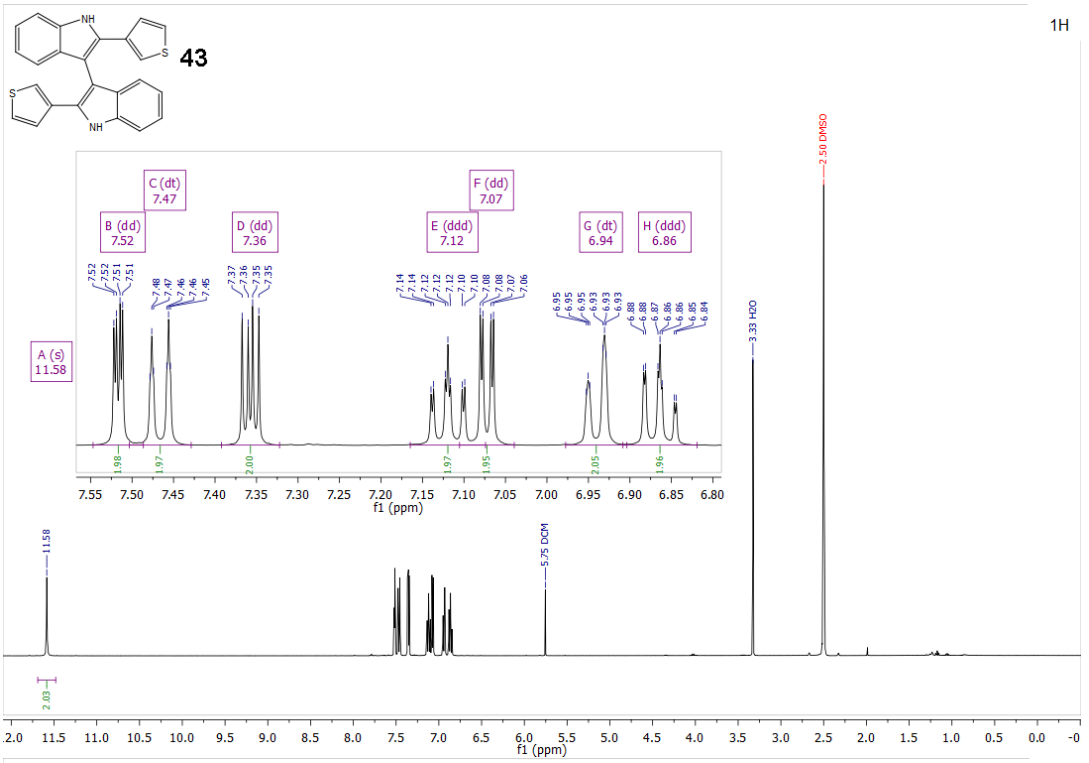


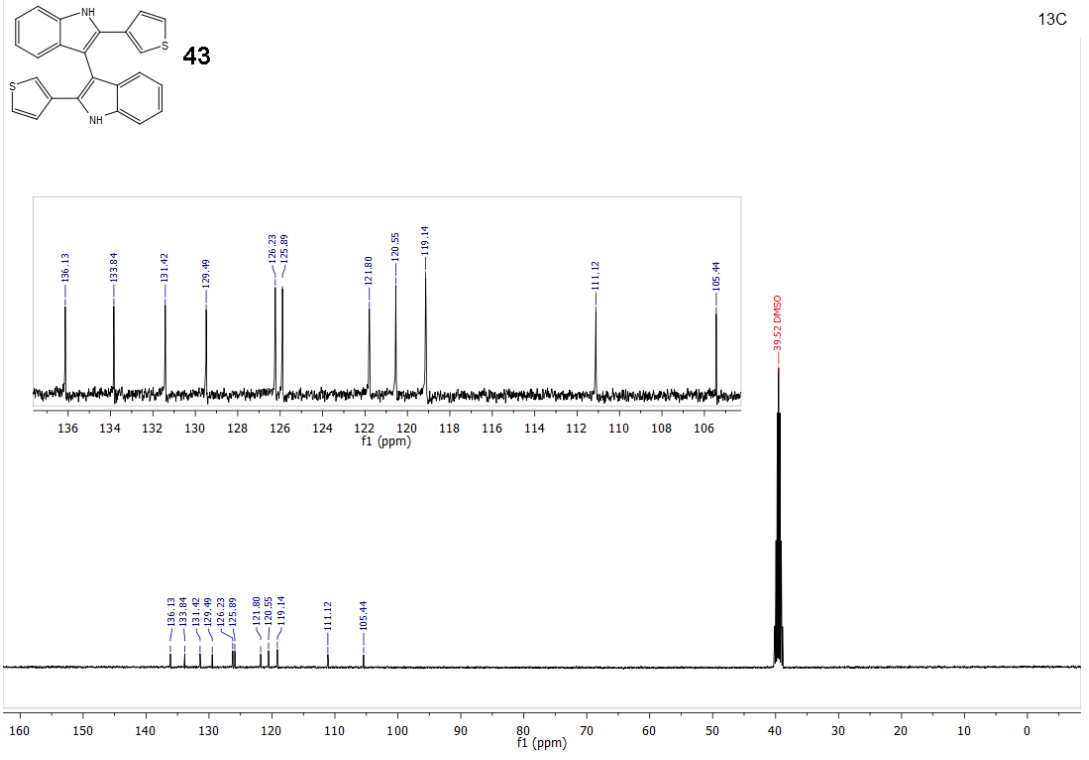
42

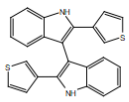
COSY


42
HSQC
f1 (ppm)
f2 (ppm)


42
HMBC
f1 (ppm)
f2 (ppm)

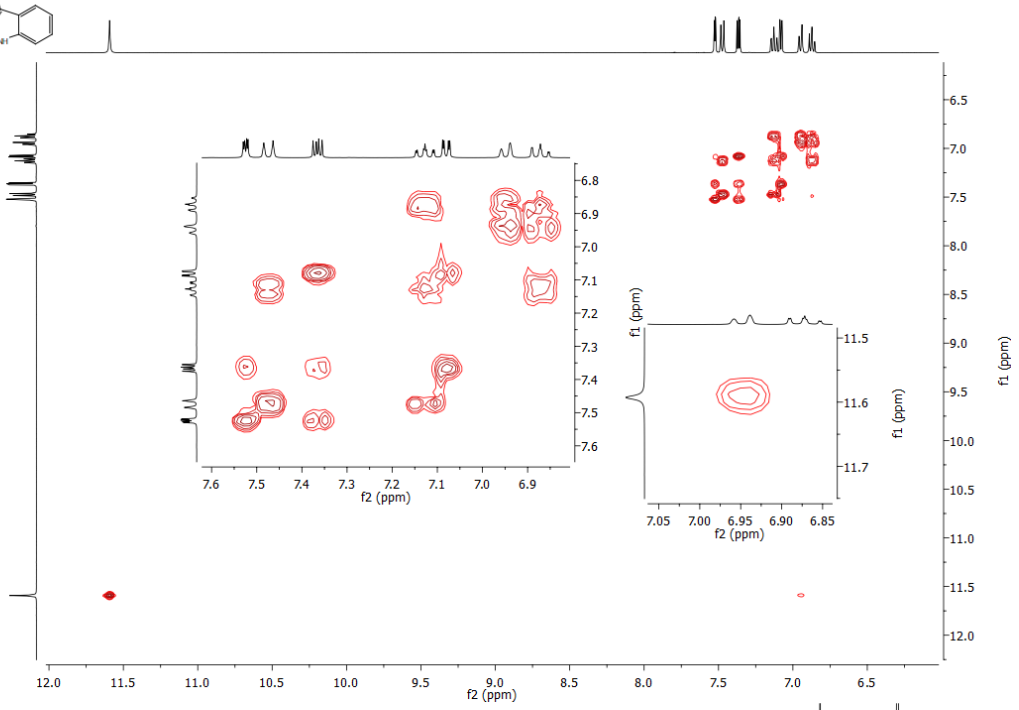

1H
43
A (s) 11.58
B (dd) 7.52
C (dt) 7.47
D (dd) 7.36
E (ddd) 7.12
F (dd) 7.07
G (dt) 6.94
H (ddd) 6.86
11.58
5.75 DCM
3.33 H2O
2.50 DMSO
f1 (ppm)

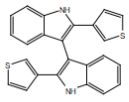

13C
43
136.13
133.84
131.42
129.49
126.23
125.89
121.80
120.55
119.14
111.12
105.44
39.52 DMSO
f1 (ppm)



43

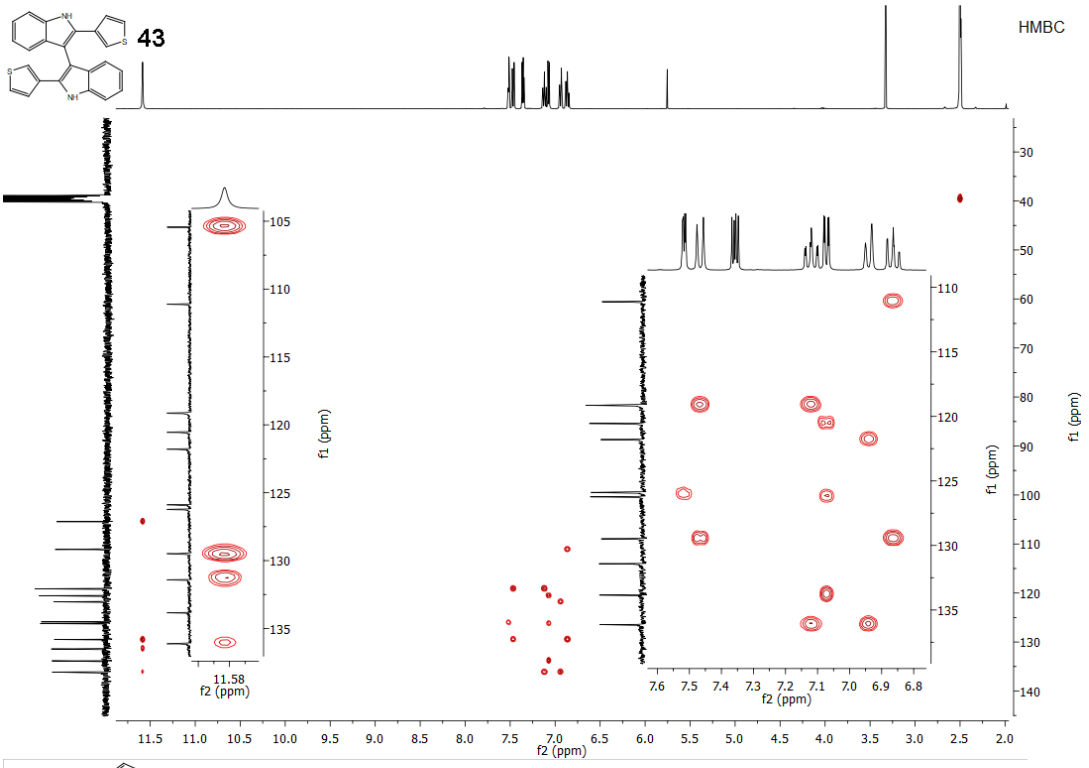
COSY

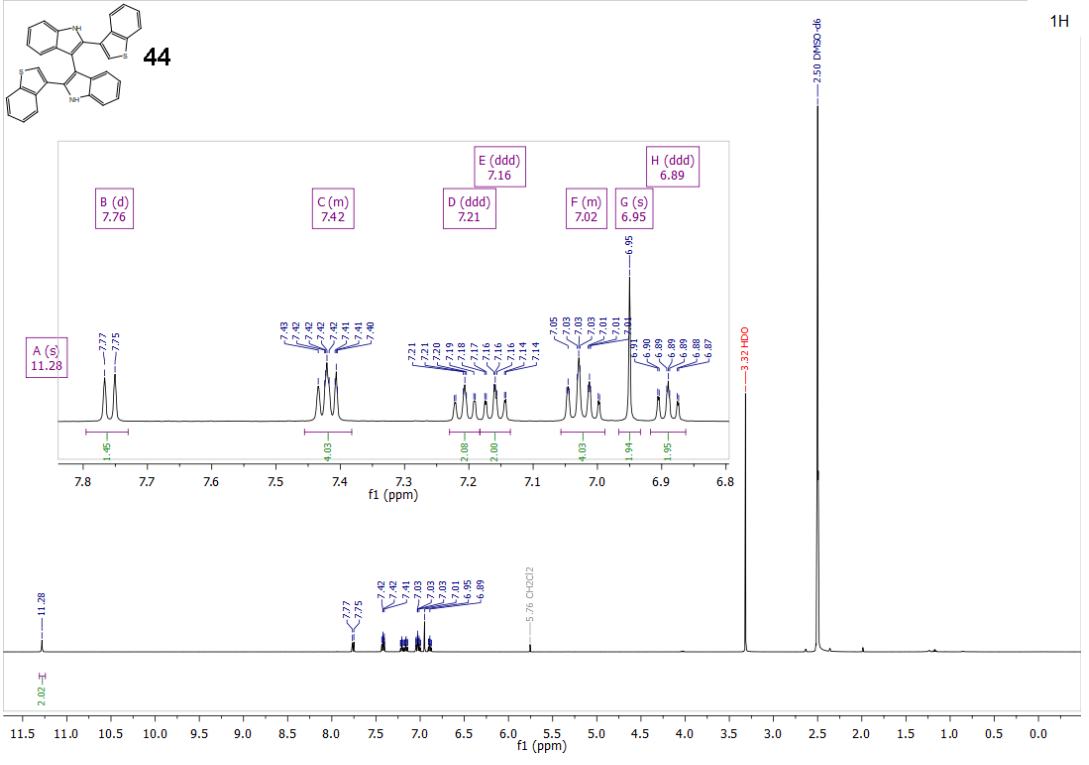


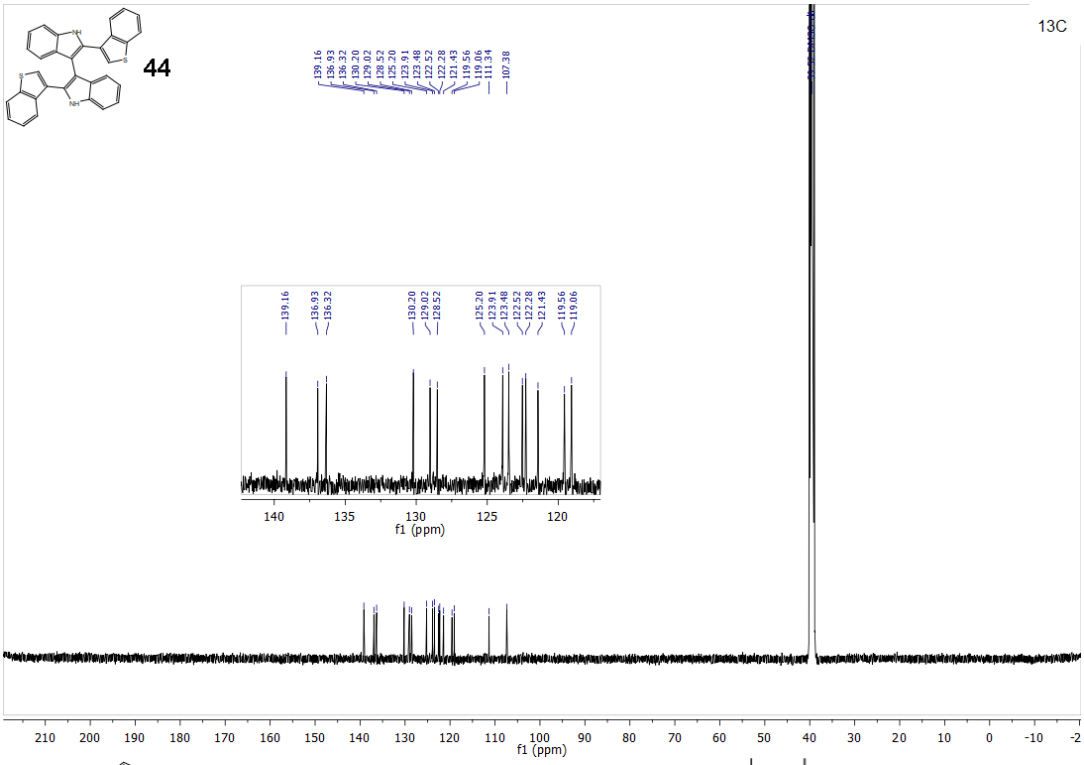


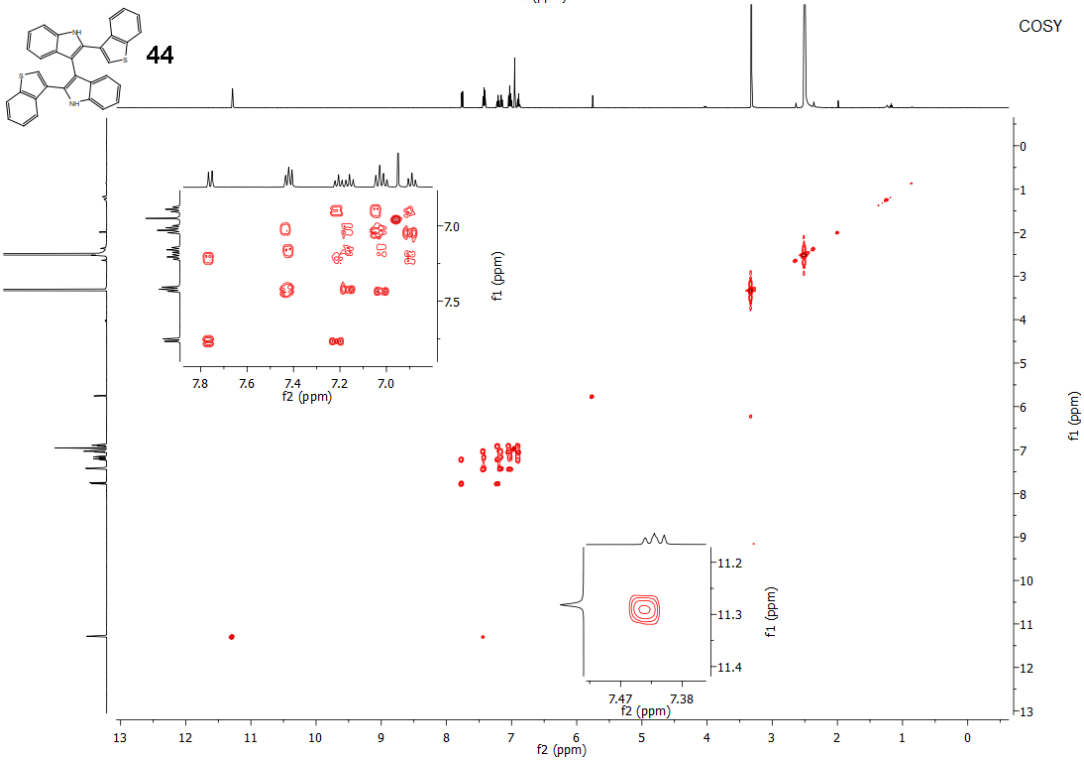
43

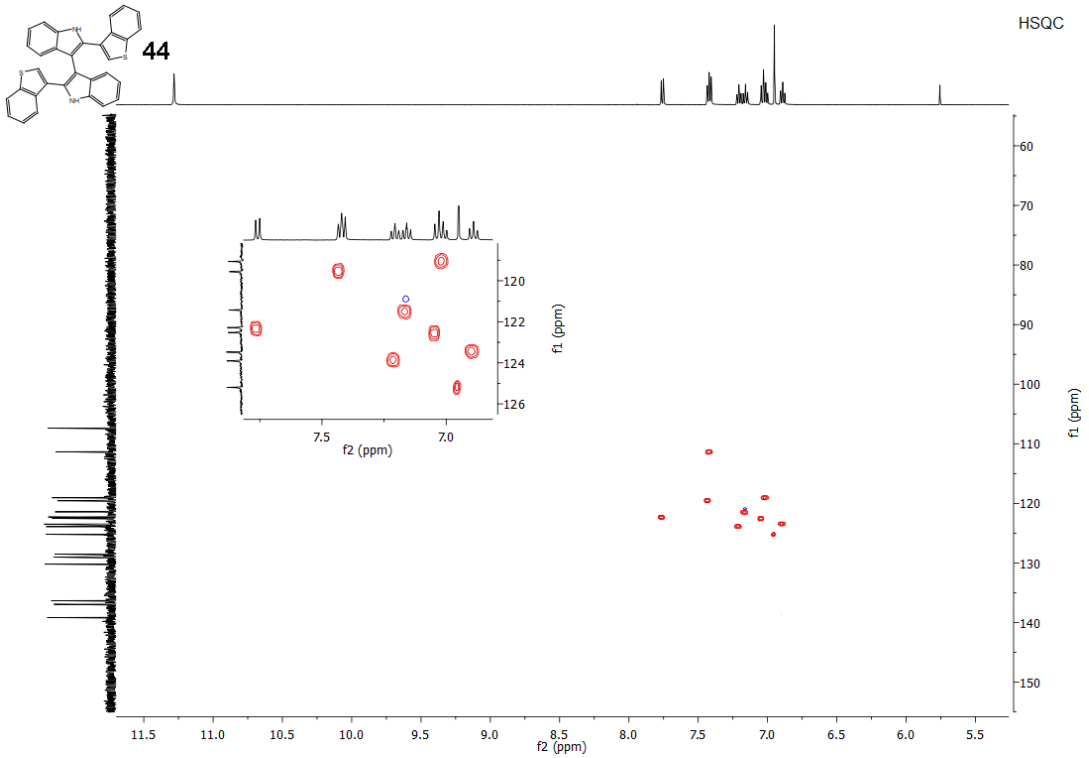
HSQC

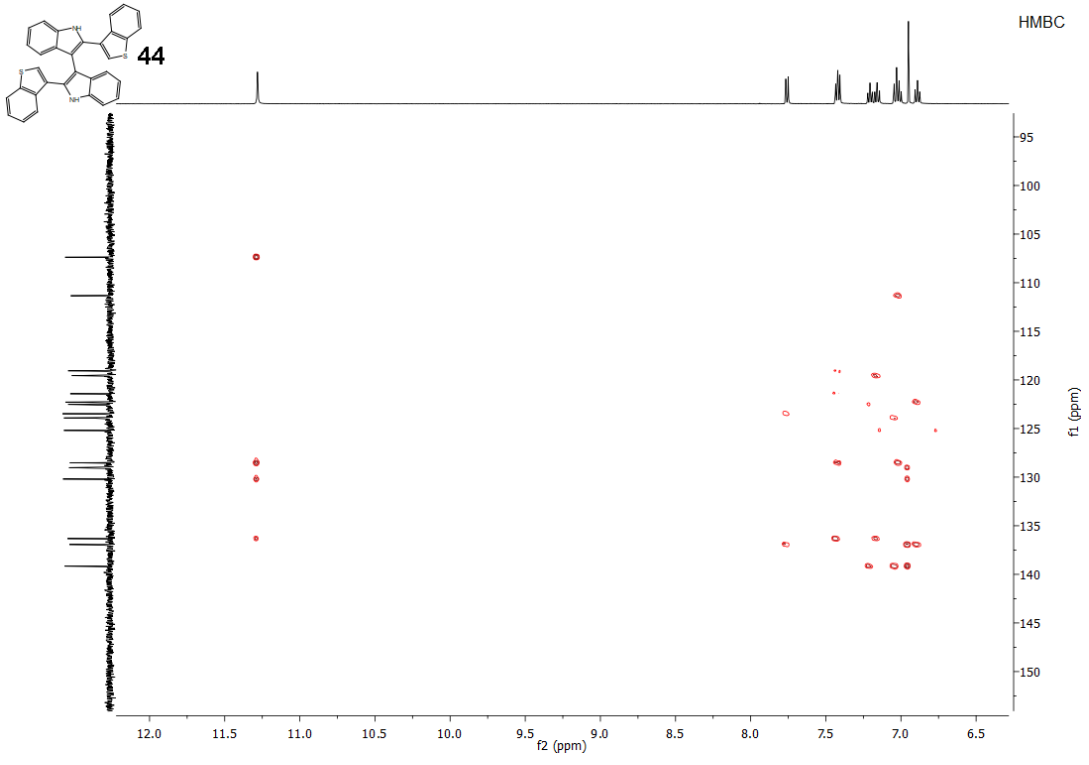

43
HMBC
f1 (ppm)
f2 (ppm)
11.58

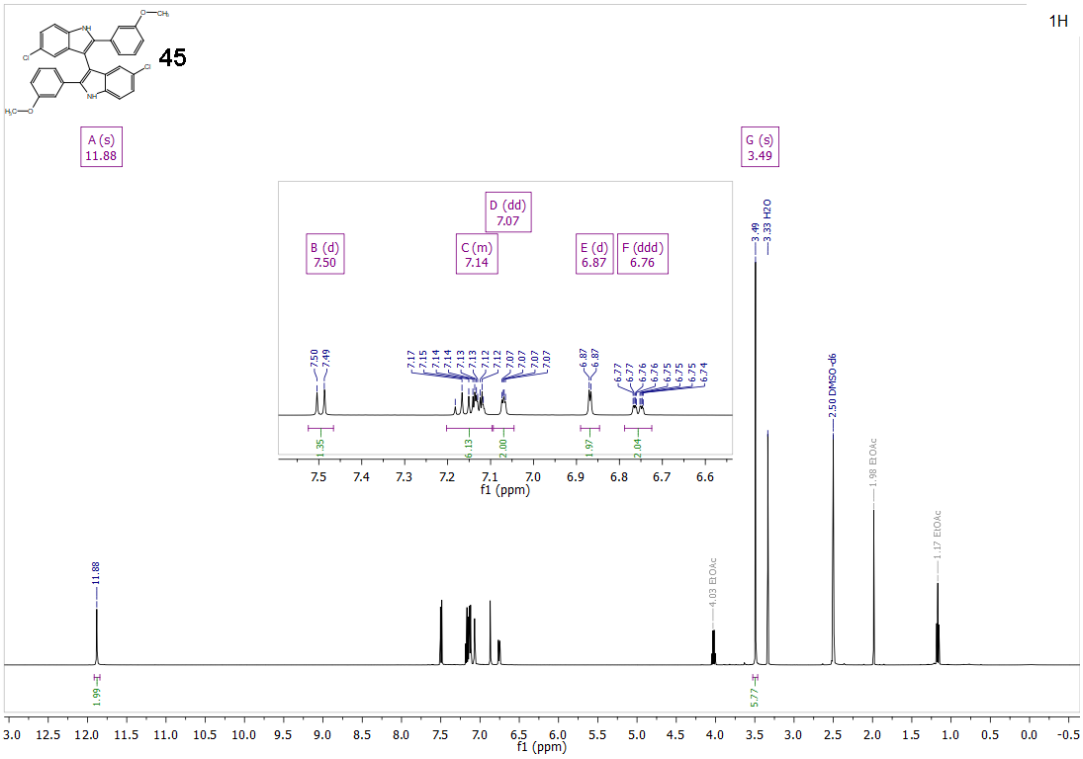

44
1H
A (s) 11.28
B (d) 7.76
C (m) 7.42
D (ddd) 7.21
E (ddd) 7.16
F (m) 7.02
G (s) 6.95
H (ddd) 6.89
2.50 DMSO-d6
3.32 HDO
5.76 CHDCl2
f1 (ppm)

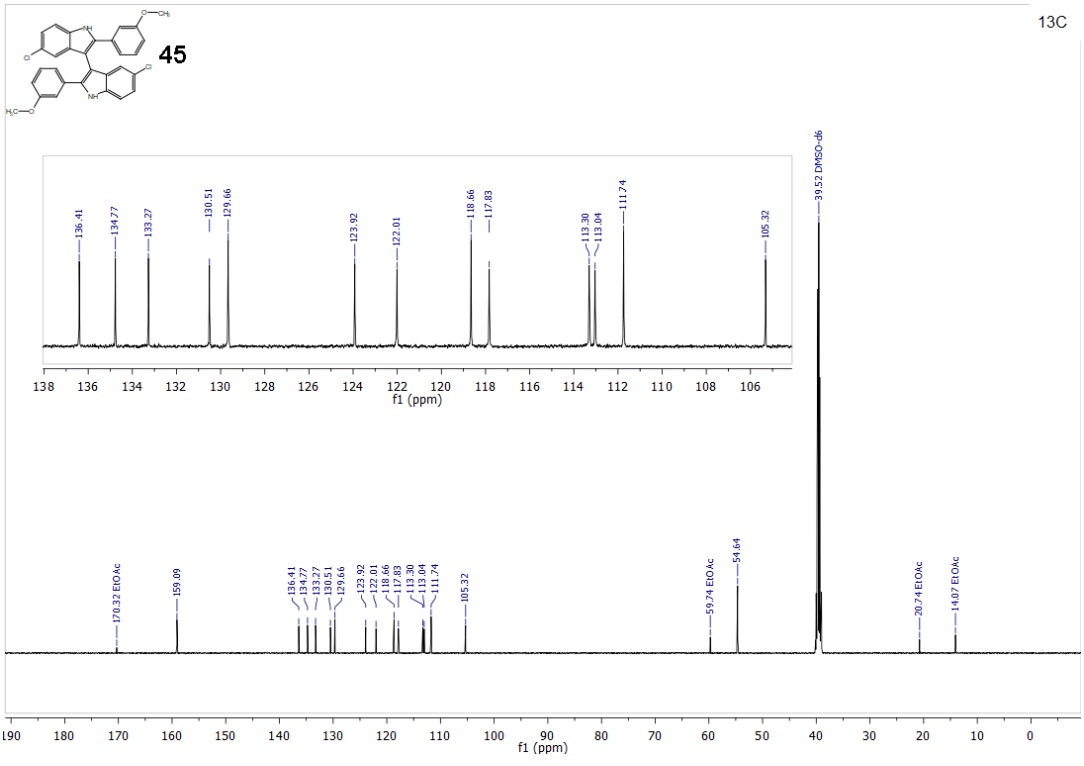

44
13C
139.16
136.93
136.32
130.20
129.02
128.52
125.20
123.91
123.48
122.52
122.28
121.43
119.56
119.06
111.34
107.38
f1 (ppm)

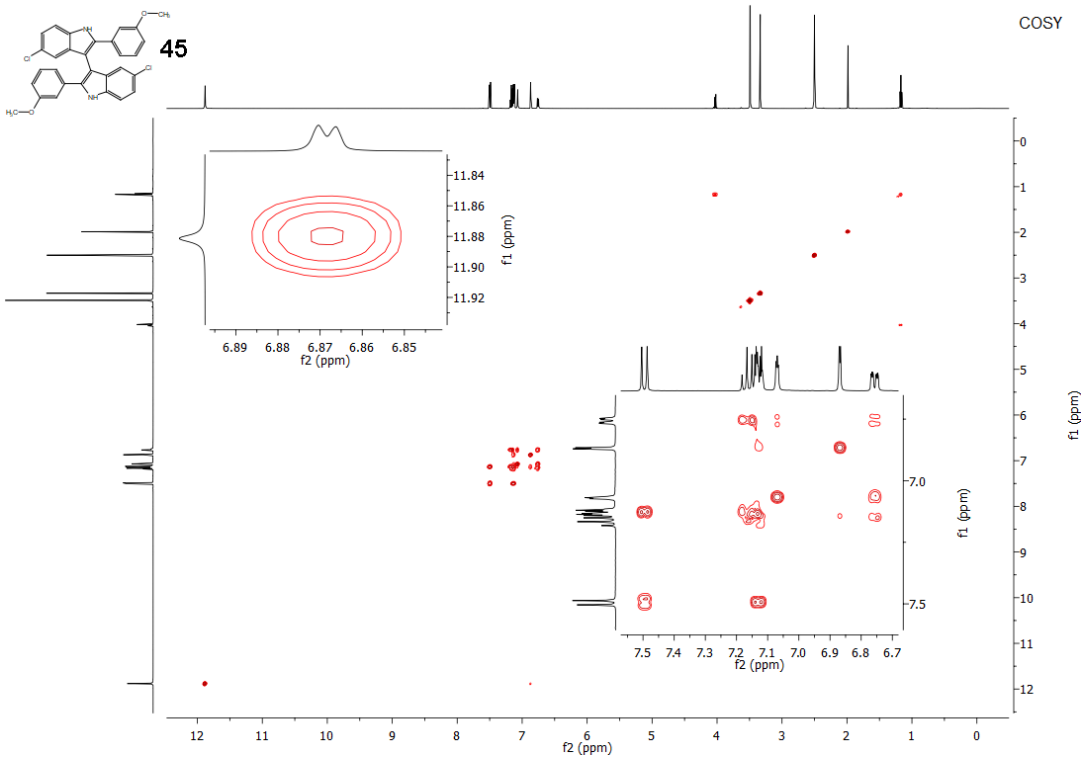

44
COSY
f1 (ppm)
f2 (ppm)

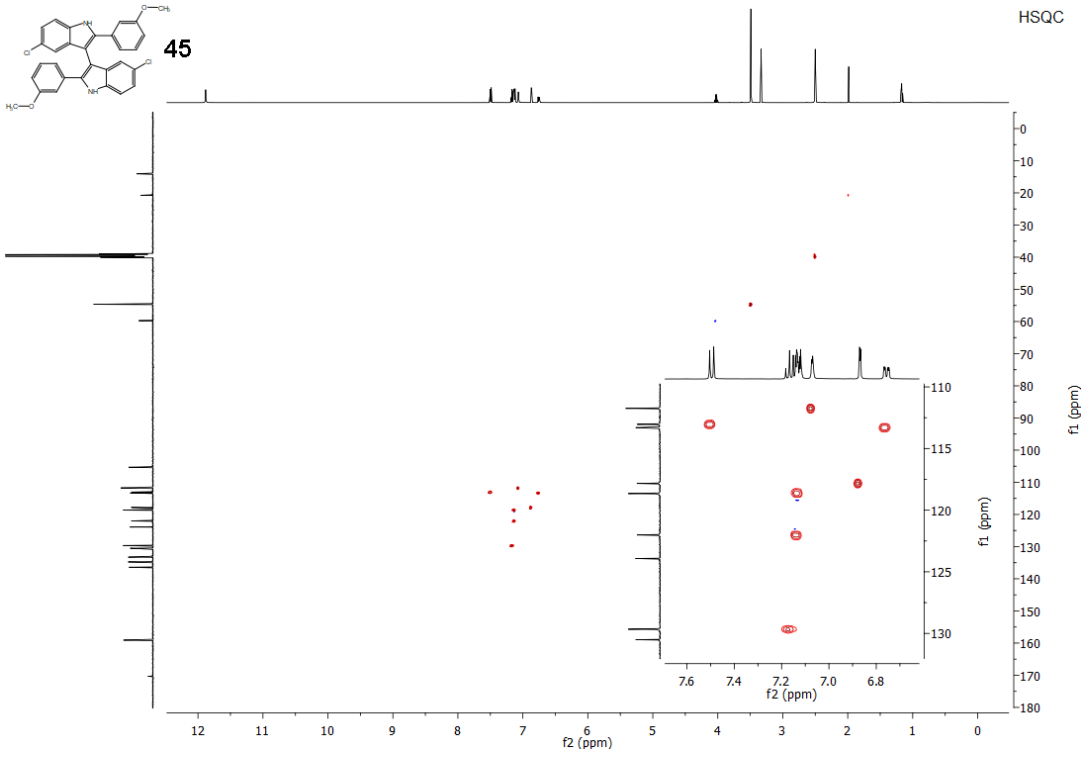

44
HSQC
f2 (ppm)
f1 (ppm)

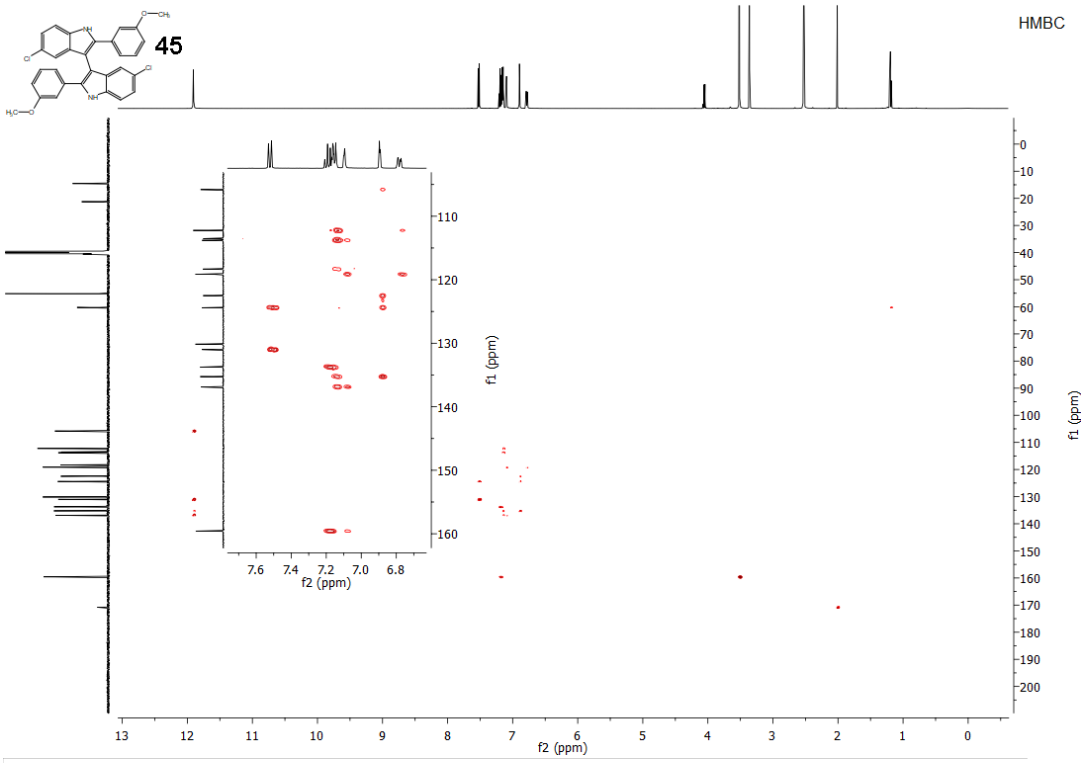

44
HMBC
f2 (ppm)
f1 (ppm)

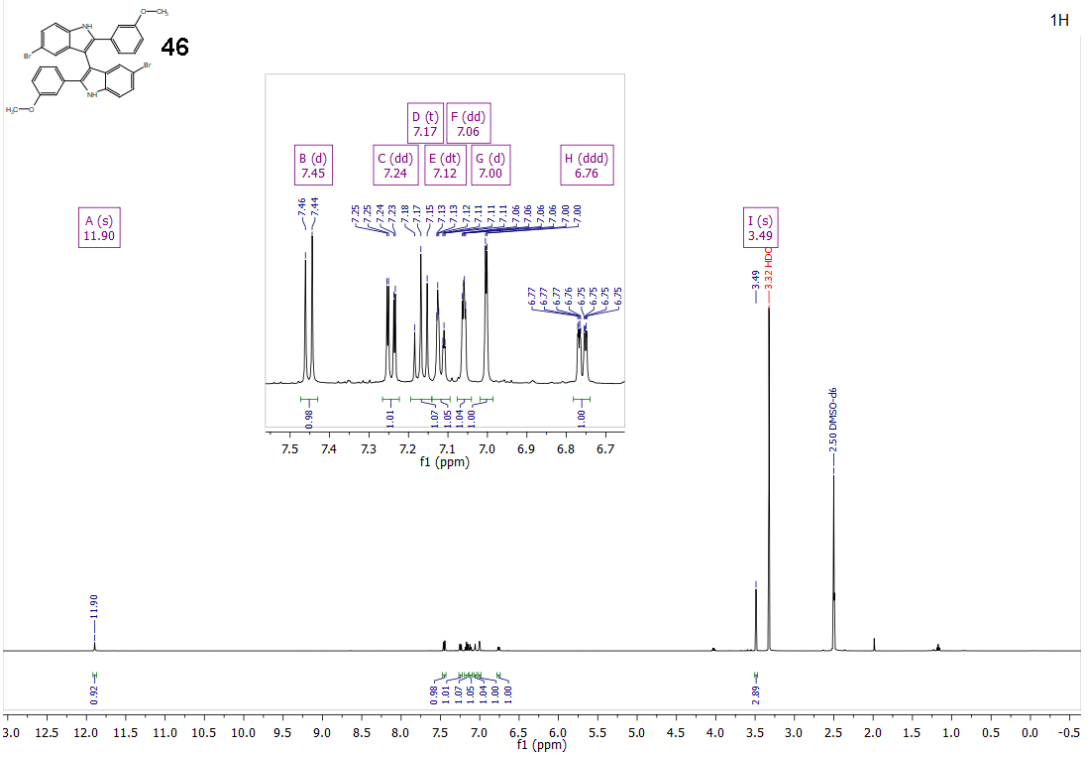

1H
45
A (s)
11.88
G (s)
3.49
B (d)
7.50
C (m)
7.14
D (dd)
7.07
E (d)
6.87
F (ddd)
6.76
3.49
3.33 H2O
2.50 DMSO-d6
1.98 EtOAc
1.17 EtOAc
4.03 EtOAc
11.88
1.99
5.77
f1 (ppm)

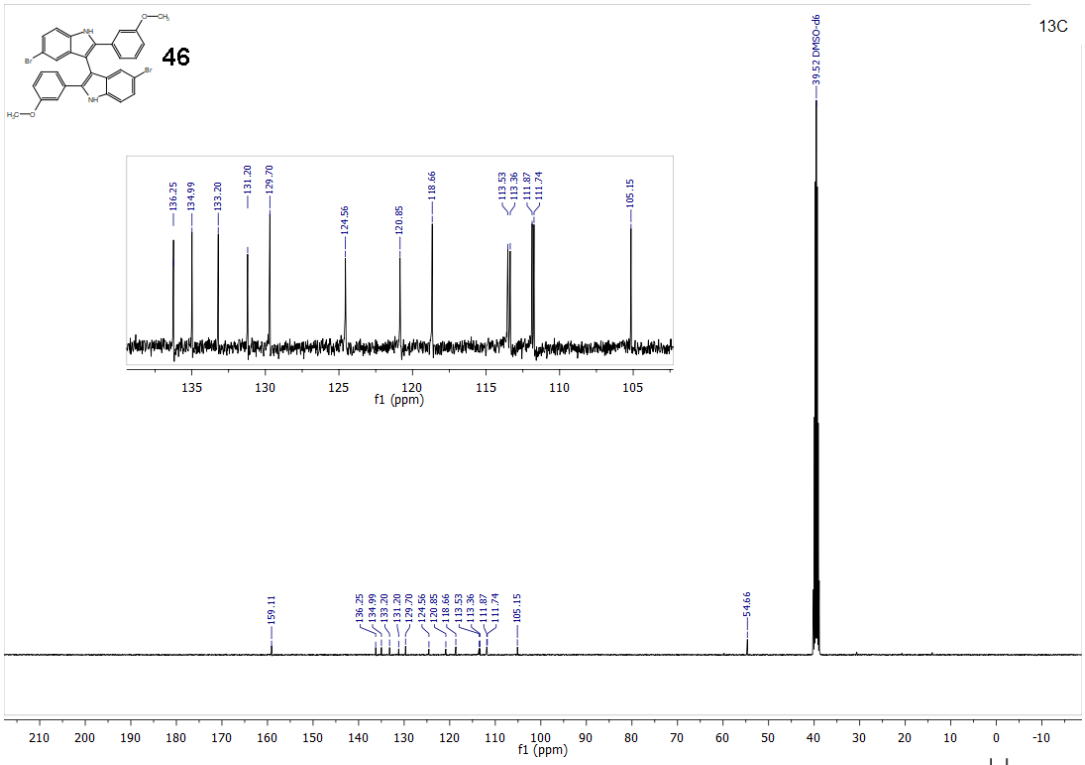

13C
45
136.41
134.77
133.27
130.51
129.66
123.92
122.01
118.66
117.83
113.30
113.04
111.74
105.32
39.52 DMSO-d6
170.32 EtOAc
159.09
59.74 EtOAc
54.64
20.74 EtOAc
14.07 EtOAc
f1 (ppm)

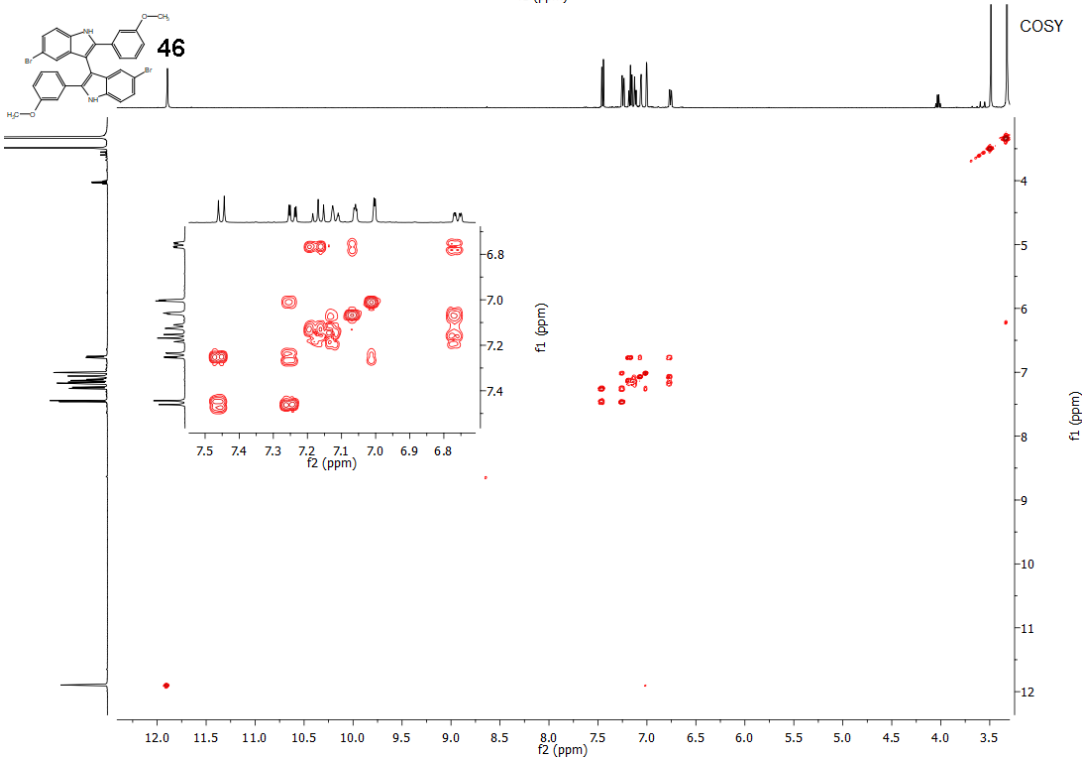

45
COSY
f1 (ppm)
f2 (ppm)

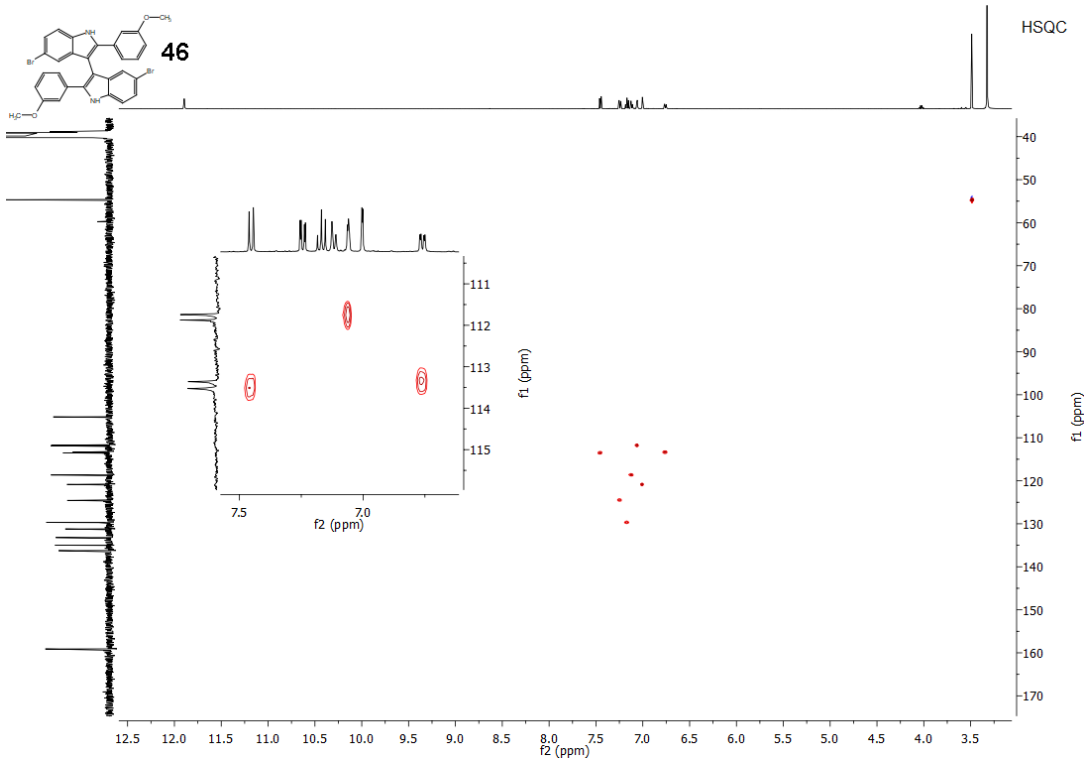

45
HSQC
f1 (ppm)
f2 (ppm)

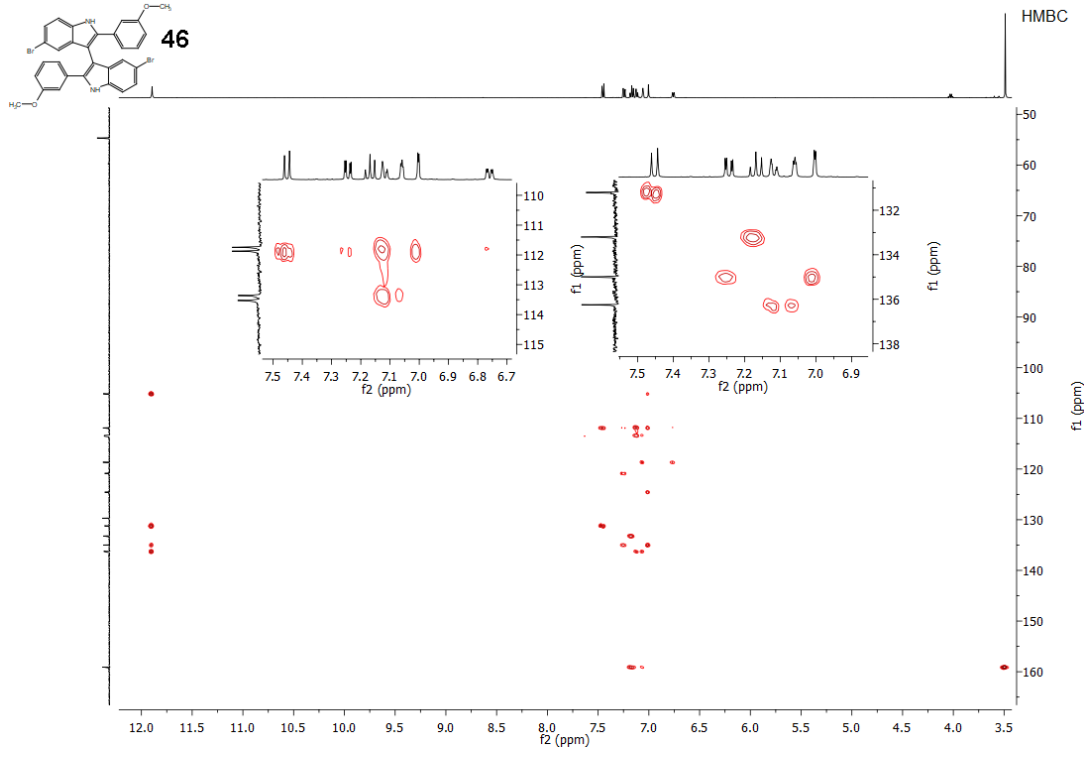

45
HMBC
f1 (ppm)
f2 (ppm)

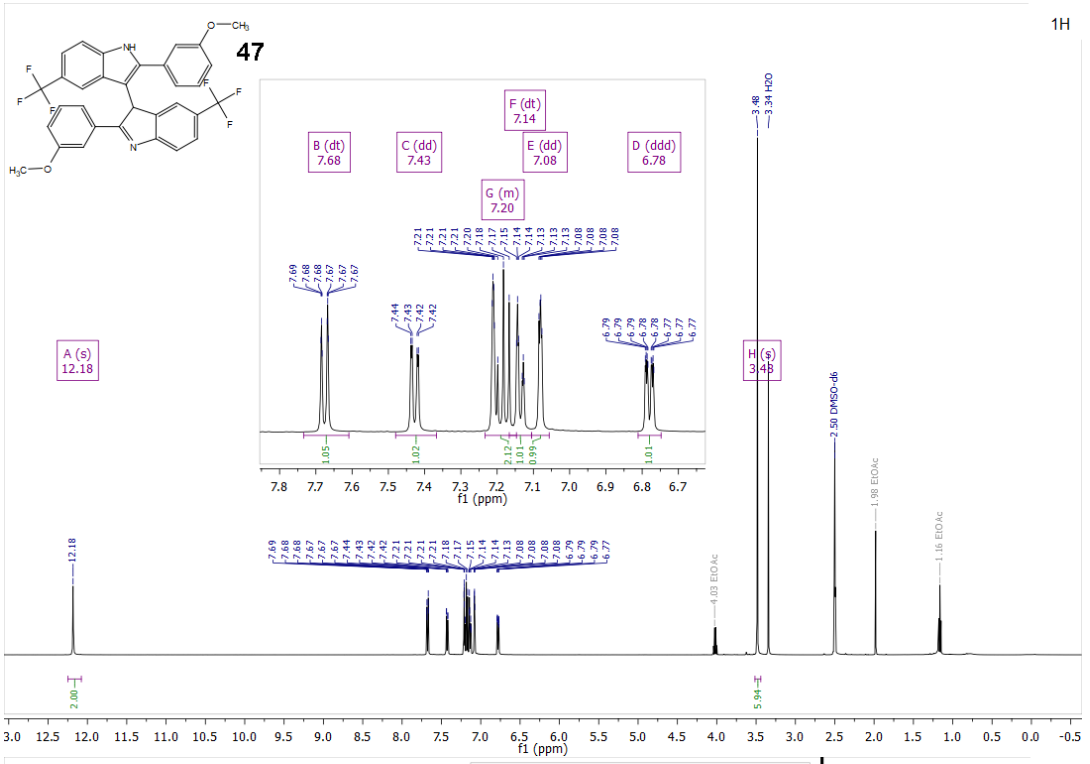

46
1H
A (s) 11.90
B (d) 7.45
C (dd) 7.24
D (t) 7.17
E (dt) 7.12
F (dd) 7.06
G (d) 7.00
H (ddd) 6.76
I (s) 3.49
3.32 HDO
2.50 DMSO-d6
f1 (ppm)

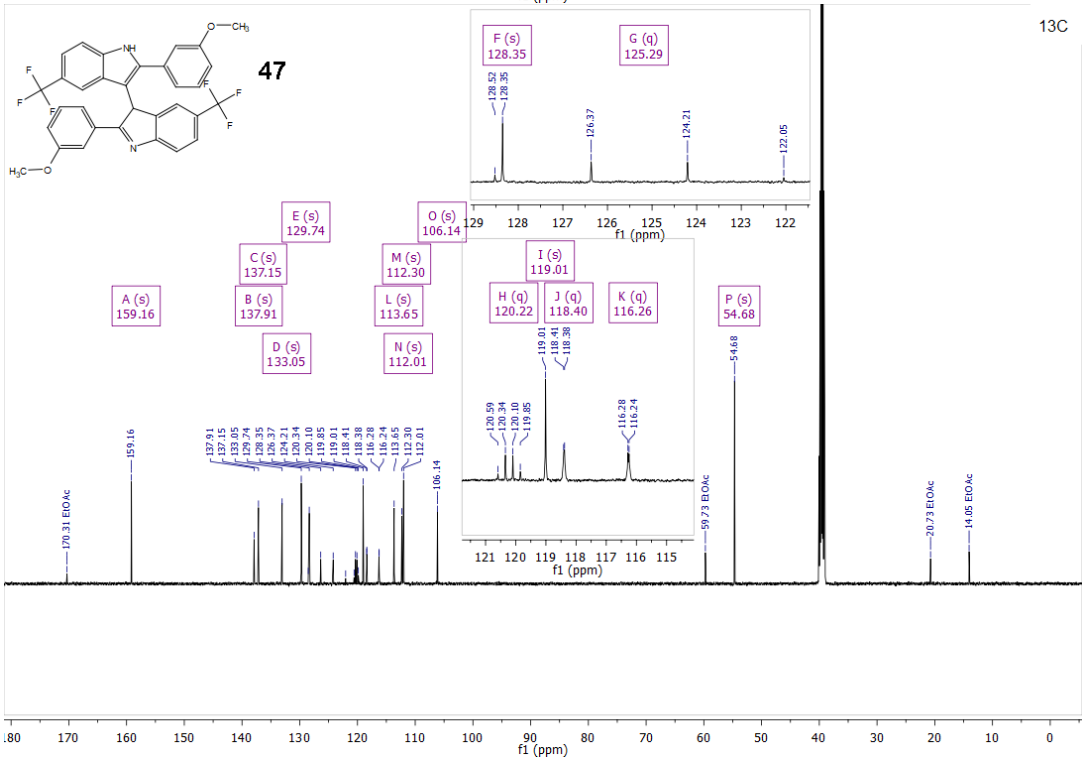

46
13C
39.52 DMSO-d6
136.25
134.99
133.20
131.20
129.70
124.56
120.85
118.66
113.53
113.36
111.87
111.74
105.15
159.11
54.66
f1 (ppm)

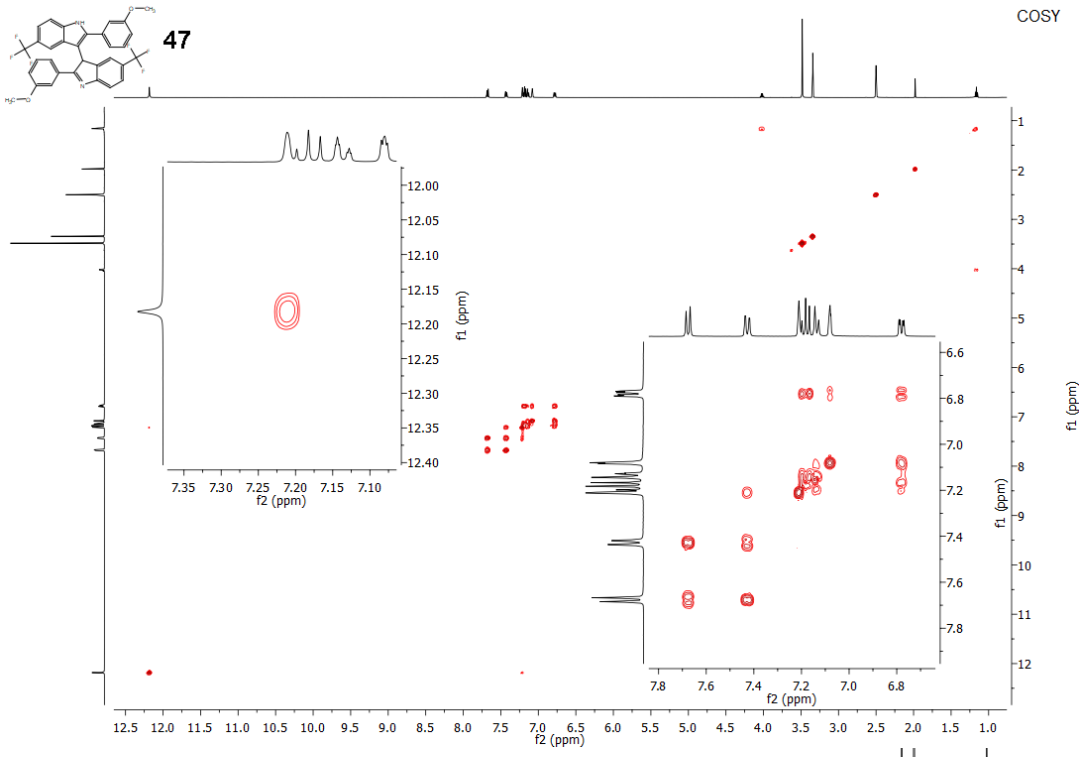

46
COSY
f1 (ppm)
f2 (ppm)

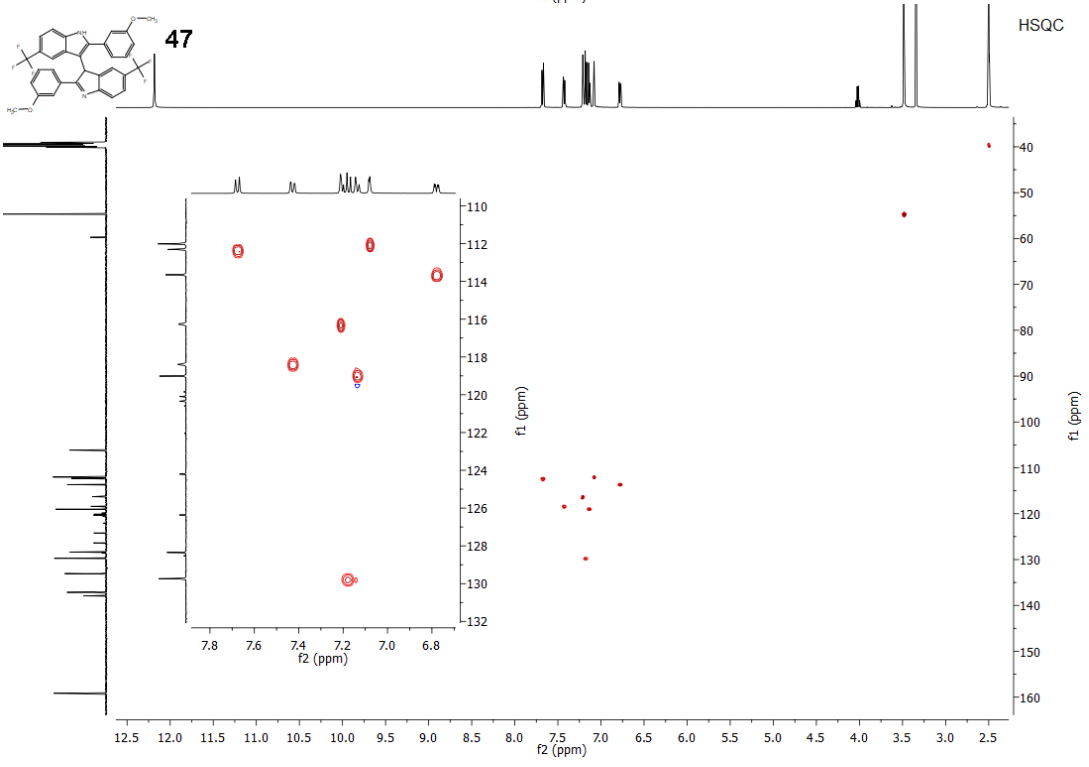

46
HSQC
f1 (ppm)
f2 (ppm)

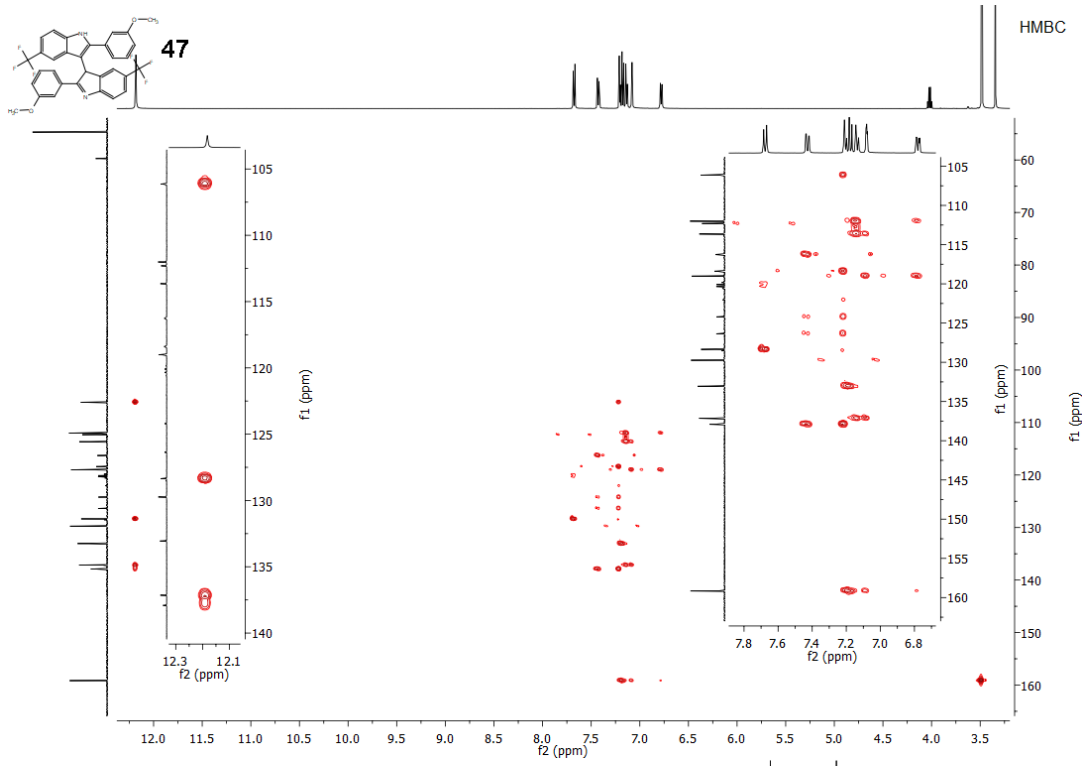

46
HMBC
f1 (ppm)
f2 (ppm)

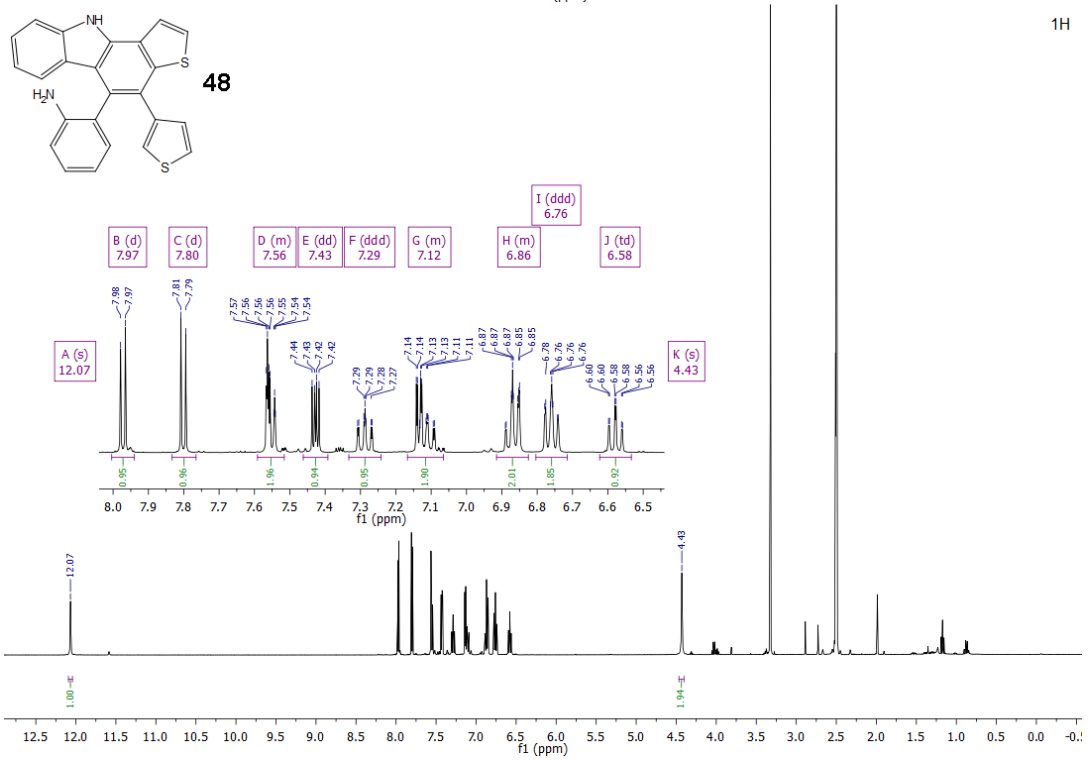

1H
47
A (s)
12.18
B (dt)
7.68
C (dd)
7.43
D (ddd)
6.78
E (dd)
7.08
F (dt)
7.14
G (m)
7.20
H (s)
3.48
3.48
3.34 H2O
2.50 DMSO-d6
1.98 EtOAc
1.16 EtOAc
4.03 EtOAc
f1 (ppm)

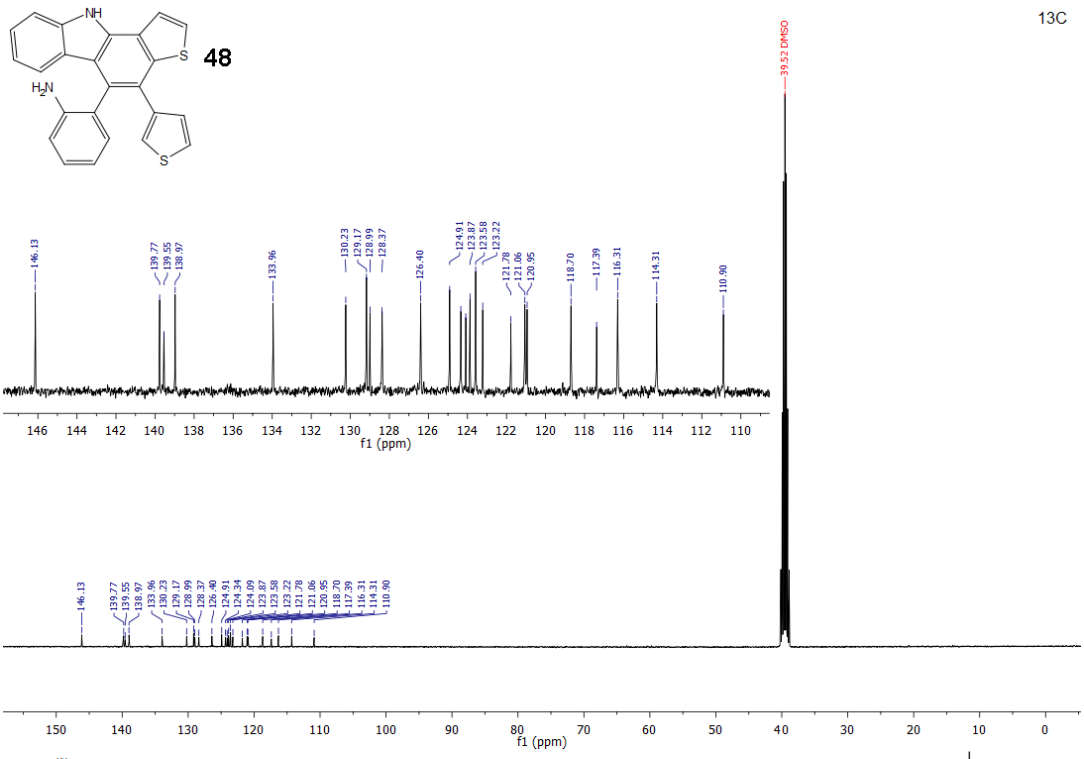

13C
47
A (s)
159.16
B (s)
137.91
C (s)
137.15
D (s)
133.05
E (s)
129.74
F (s)
128.35
G (q)
125.29
H (q)
120.22
I (s)
119.01
J (q)
118.40
K (q)
116.26
L (s)
113.65
M (s)
112.30
N (s)
112.01
O (s)
106.14
P (s)
54.68
170.31 EtOAc
59.73 EtOAc
20.73 EtOAc
14.05 EtOAc
f1 (ppm)

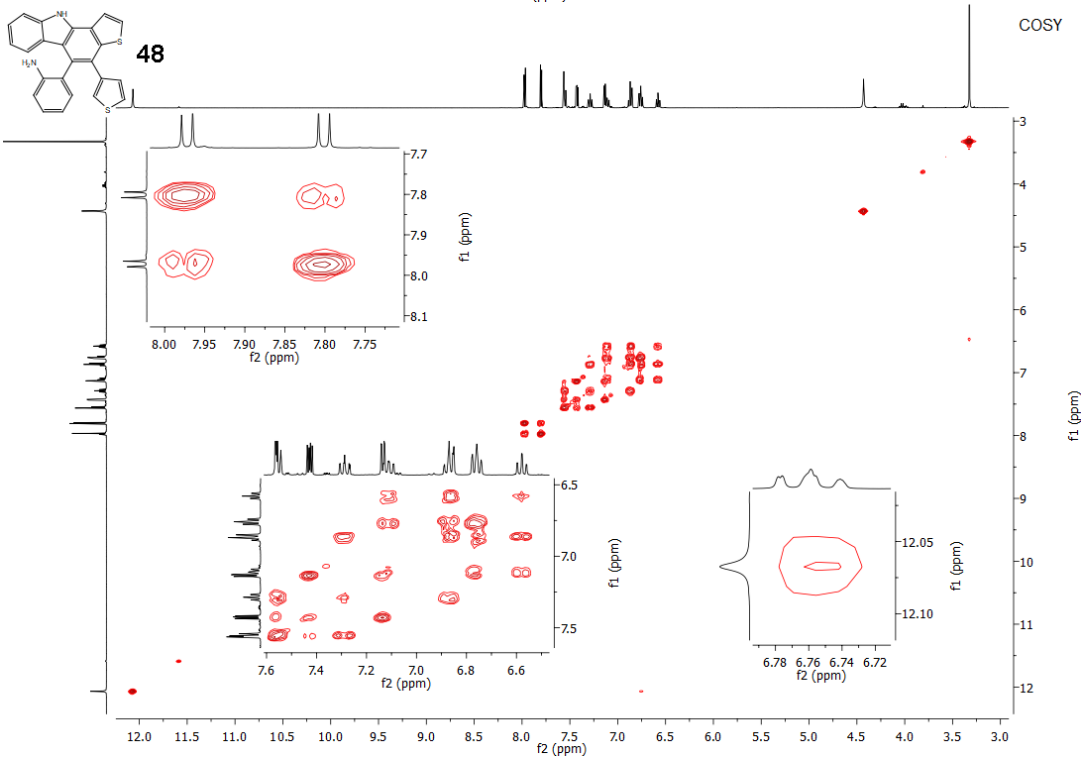

47
COSY
f1 (ppm)
f2 (ppm)

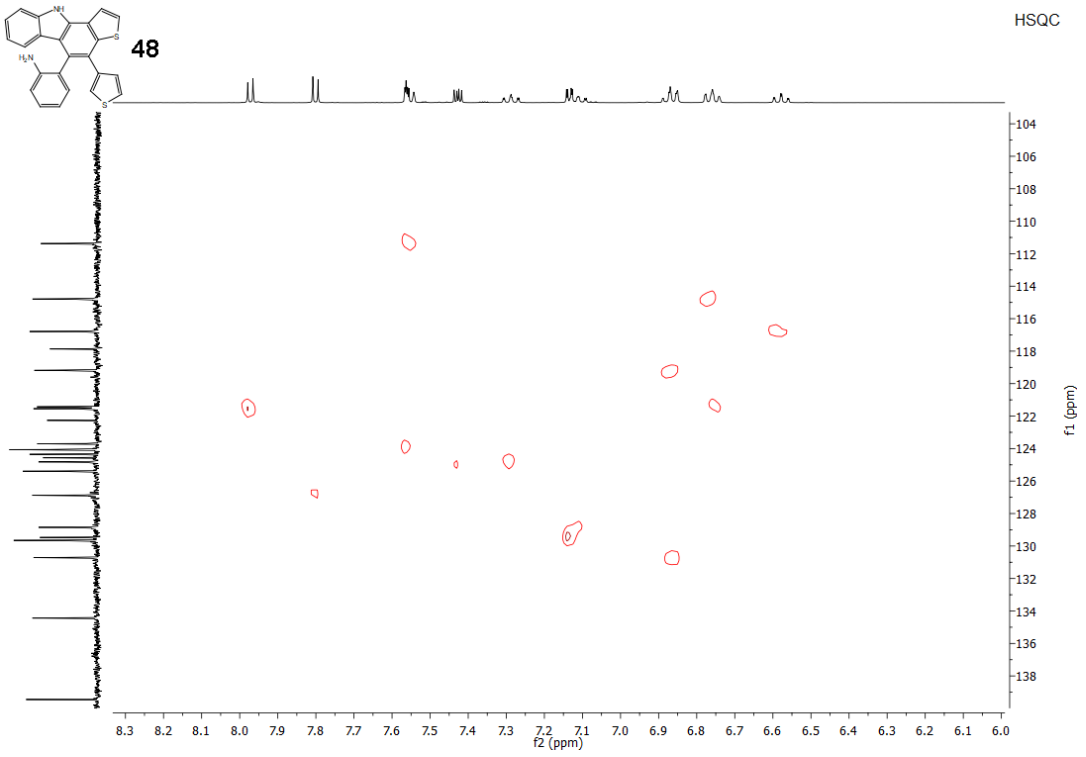

47
HSQC
f1 (ppm)
f2 (ppm)

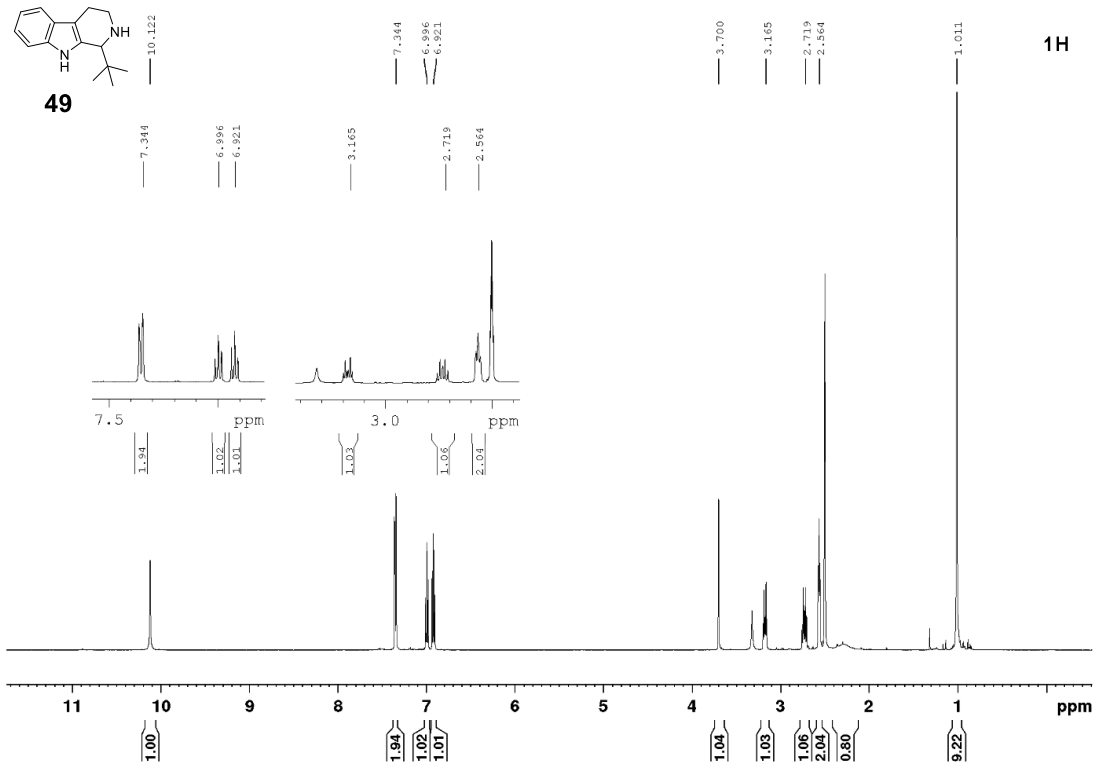

47
HMBC
f1 (ppm)
f2 (ppm)

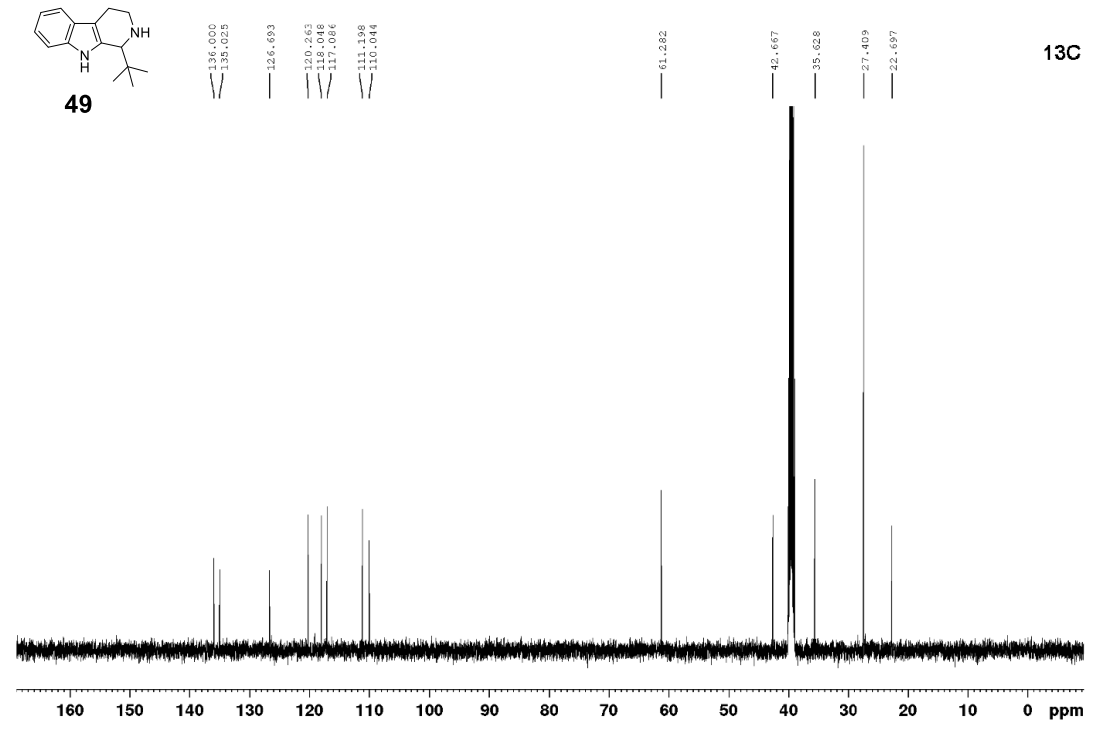

48
1H
A (s) 12.07
B (d) 7.97
C (d) 7.80
D (m) 7.56
E (dd) 7.43
F (ddd) 7.29
G (m) 7.12
H (m) 6.86
I (ddd) 6.76
J (td) 6.58
K (s) 4.43
f1 (ppm)

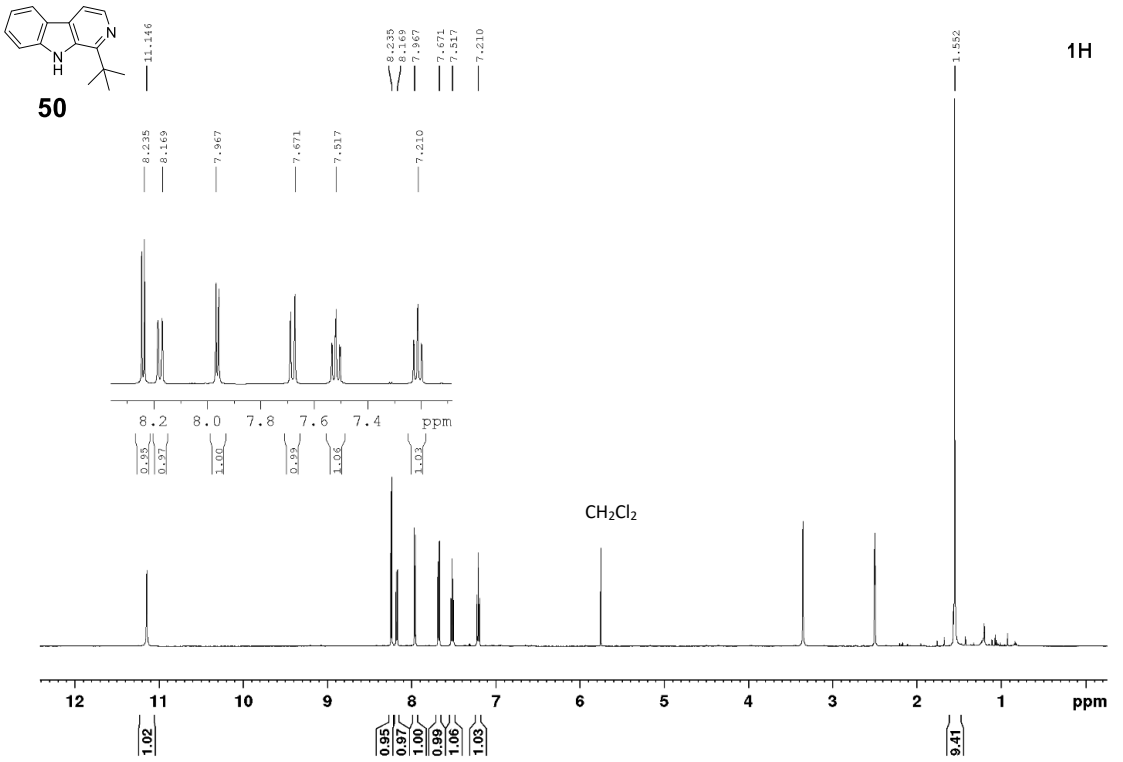

48
13C
39.52 DMSO
146.13
139.77
139.55
138.97
133.96
130.23
129.17
128.99
128.37
126.40
124.91
123.87
123.58
123.22
121.78
121.06
120.95
118.70
117.39
116.31
114.31
110.90
f1 (ppm)

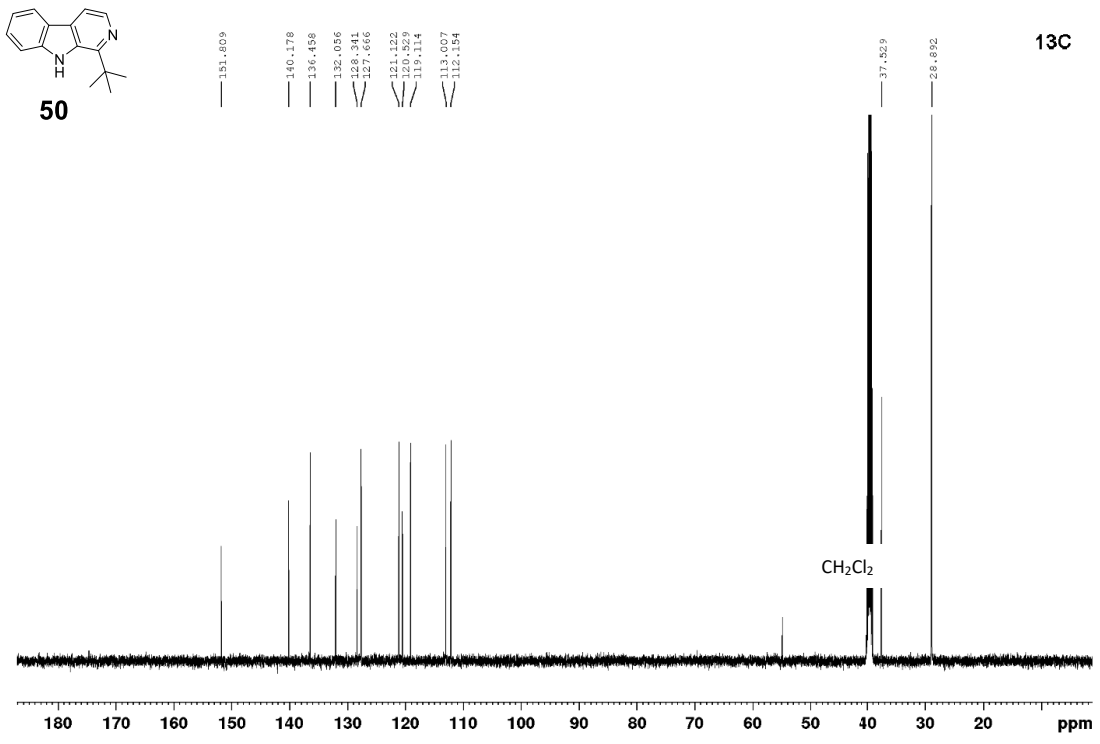

48
COSY
f1 (ppm)
f2 (ppm)

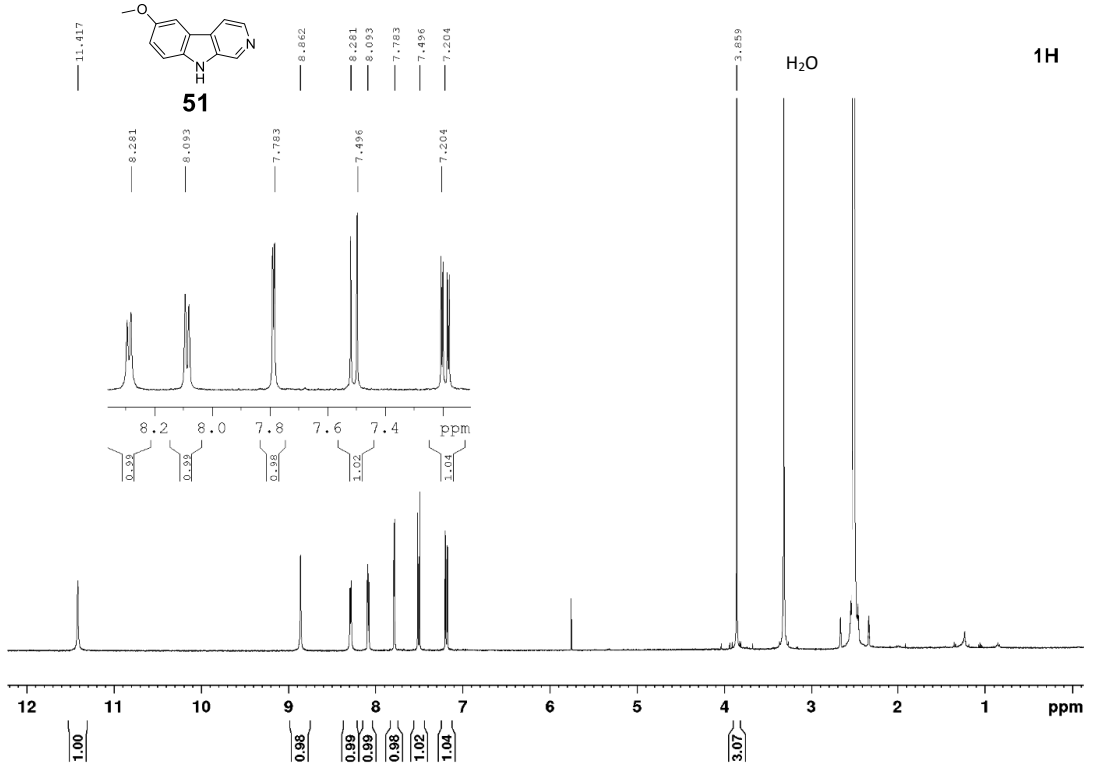

48
HSQC
f1 (ppm)
f2 (ppm)

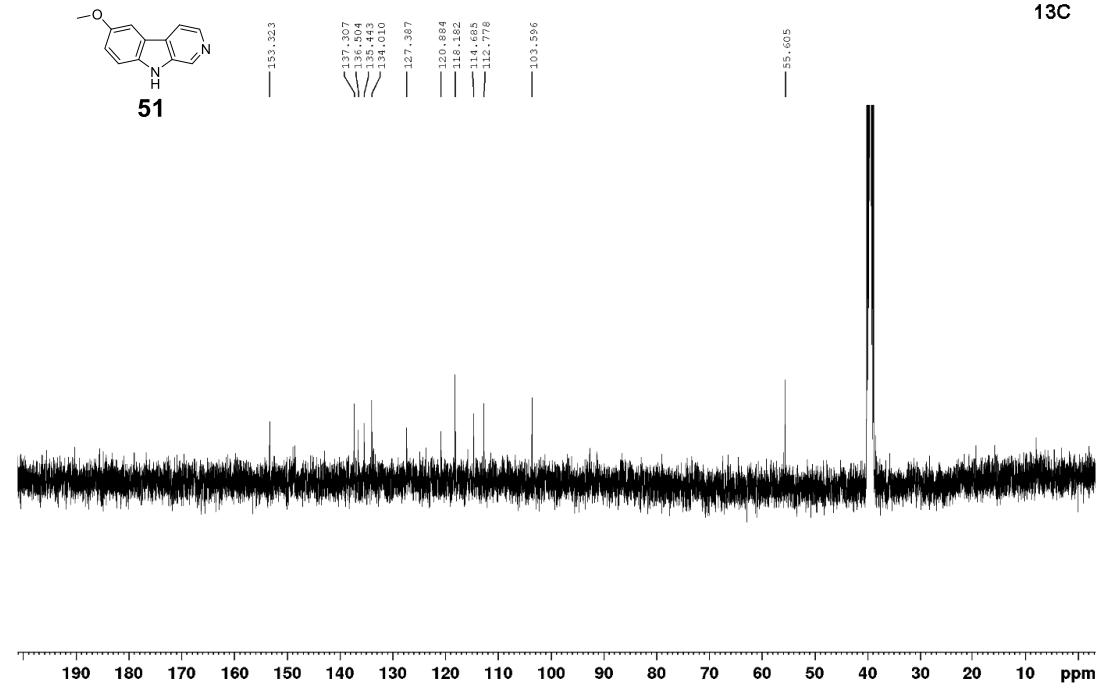

49
1H
10.122
7.344
6.996
6.921
3.700
3.165
2.719
2.564
1.011
7.5
ppm
3.0
ppm
1.94
1.02
1.01
1.03
1.06
2.04
ppm
1.00
1.94
1.02
1.01
1.04
1.03
1.06
2.04
0.80
9.22

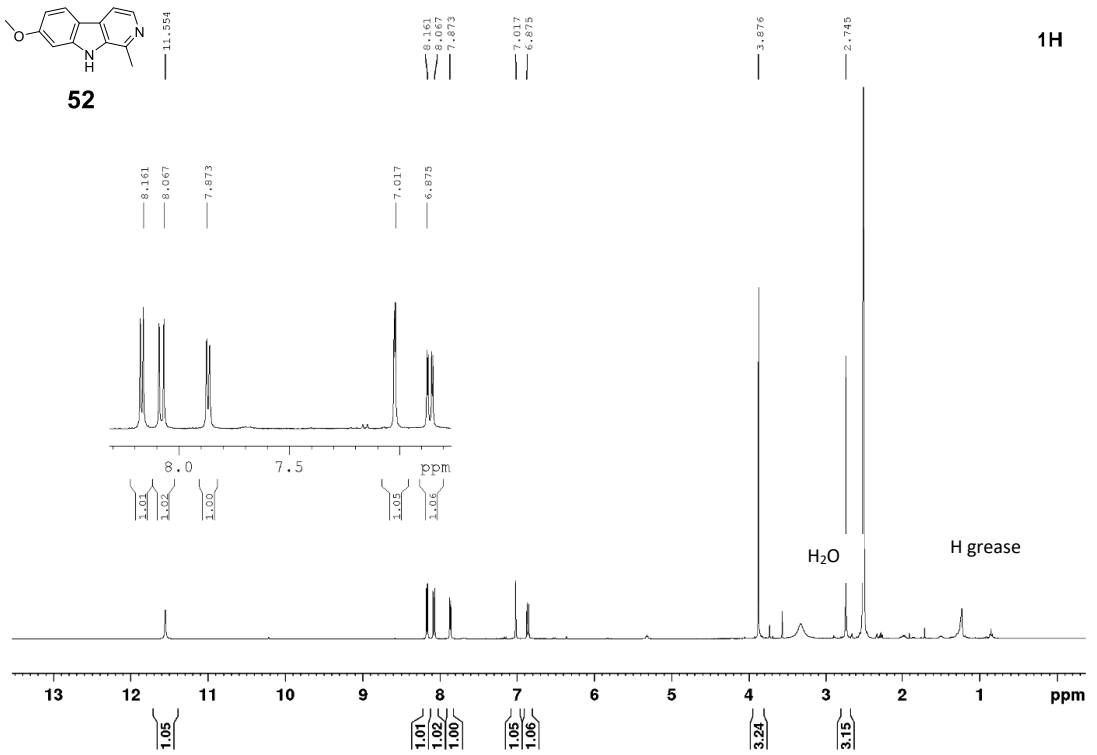

49
13C
136.000
135.025
126.693
120.263
118.048
117.086
111.198
110.044
61.282
42.667
35.628
27.409
22.697
ppm

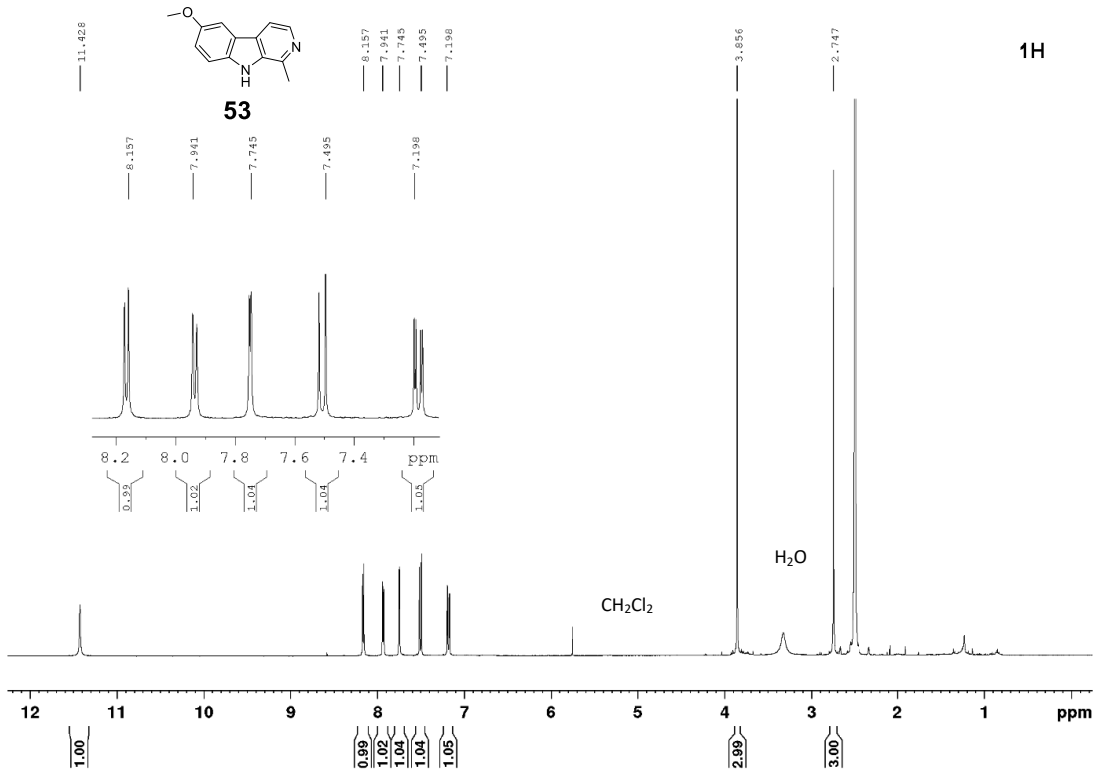

50
1H
11.146
8.235
8.169
7.967
7.671
7.517
7.210
1.552
CH2Cl2
8.2
8.0
7.8
7.6
7.4
ppm
0.95
0.97
1.00
0.99
1.06
1.03
1.02
9.41
12
11
10
9
8
7
6
5
4
3
2
1
ppm

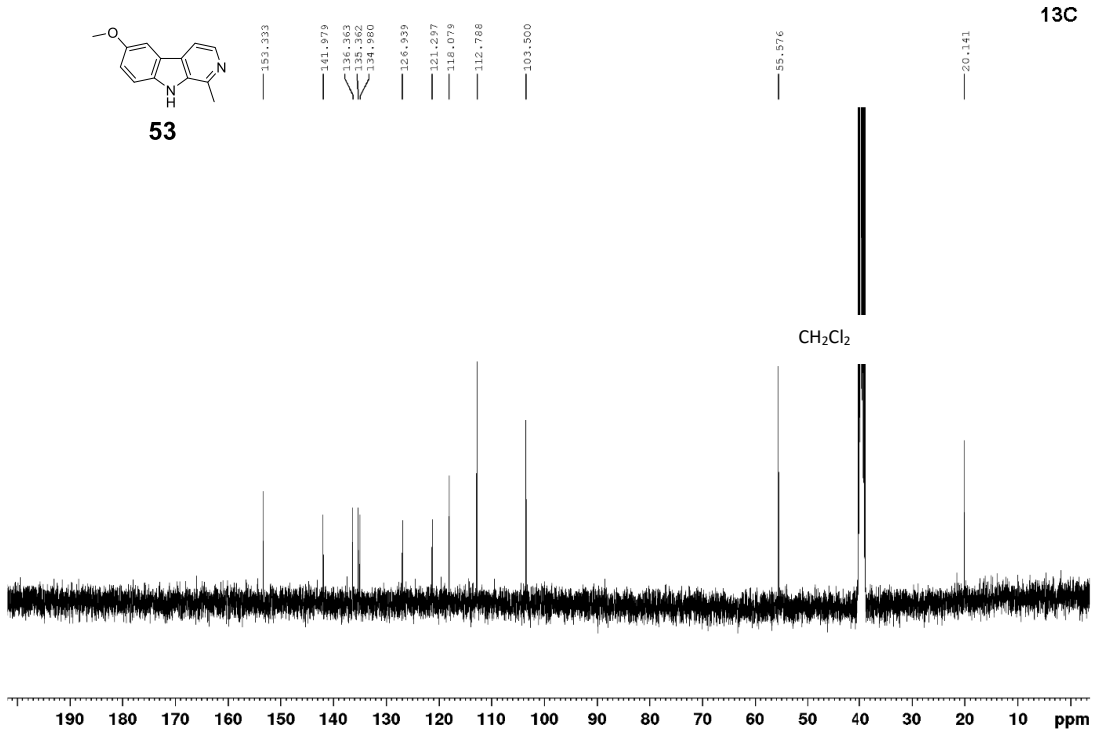

50
13C
151.809
140.178
136.458
132.056
128.341
127.666
121.122
120.529
119.114
113.007
112.154
37.529
28.892
CH2Cl2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

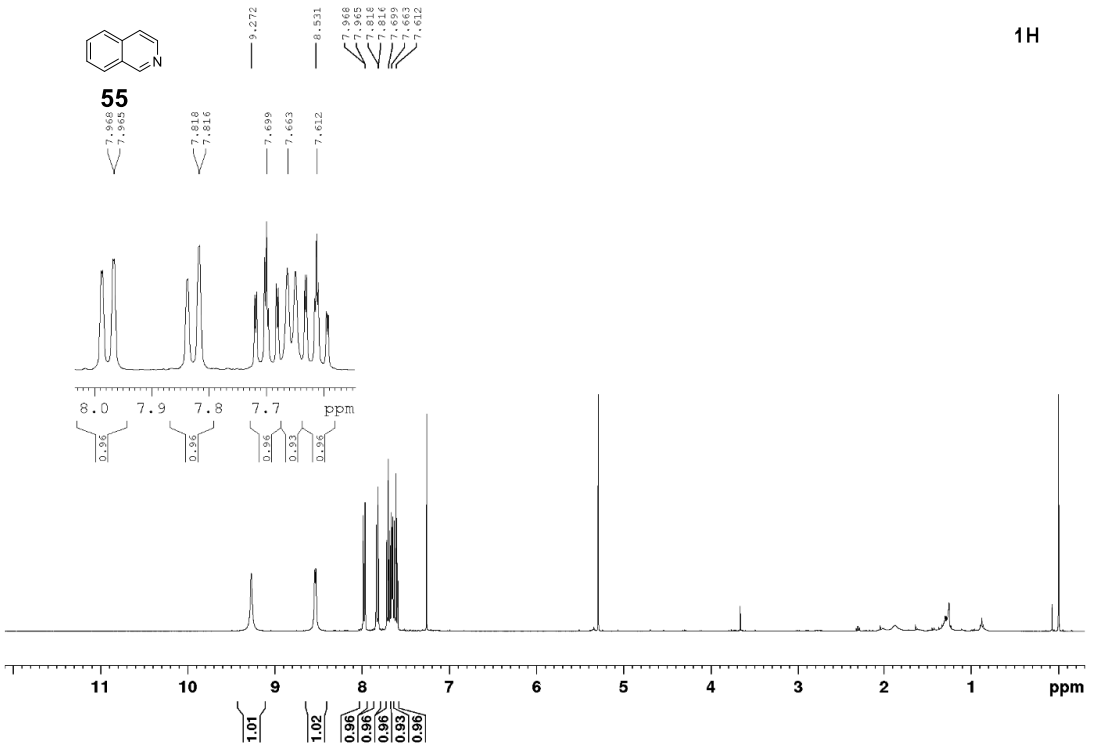

11.417
8.862
8.281
8.093
7.783
7.496
7.204
3.859
H2O
1H
51
8.2
8.0
7.8
7.6
7.4
ppm
0.99
0.99
0.98
1.02
1.04
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.98
0.99
0.99
0.98
1.02
1.04
3.07

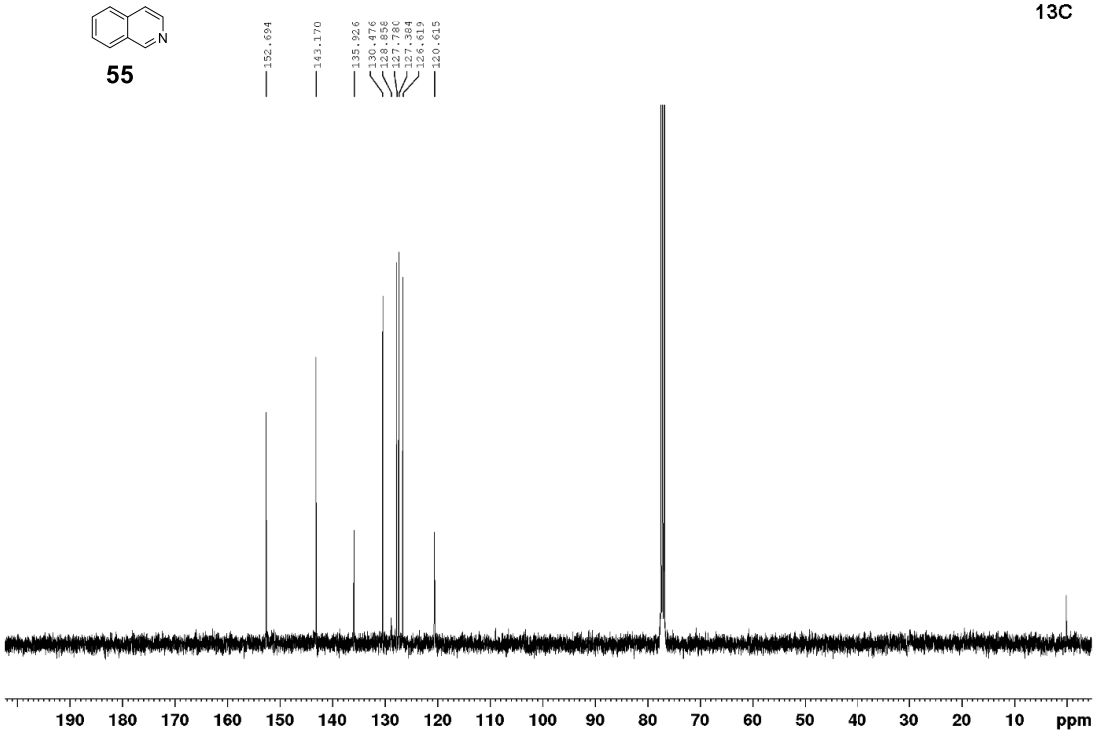

13C
51
153.323
137.307
136.904
135.443
134.010
127.387
120.884
116.182
114.685
112.778
103.596
55.605
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


52
1H
11.554
8.161
8.067
7.873
7.017
6.875
3.876
2.745
H2O
H grease
ppm
52
13C
160.329
142.281
140.823
136.781
134.427
127.702
122.799
114.698
112.130
109.394
94.544
55.349
19.849
ppm


1H
53
11.428
8.157
7.961
7.745
7.495
7.198
3.856
2.747
8.2
8.0
7.8
7.6
7.4
ppm
0.99
1.02
1.04
1.04
1.05
H2O
CH2Cl2
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.99
1.02
1.04
1.04
1.05
2.99
3.00


13C
53
153.333
141.979
136.363
135.322
134.980
126.939
121.297
118.079
112.788
103.500
55.576
20.141
CH2Cl2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

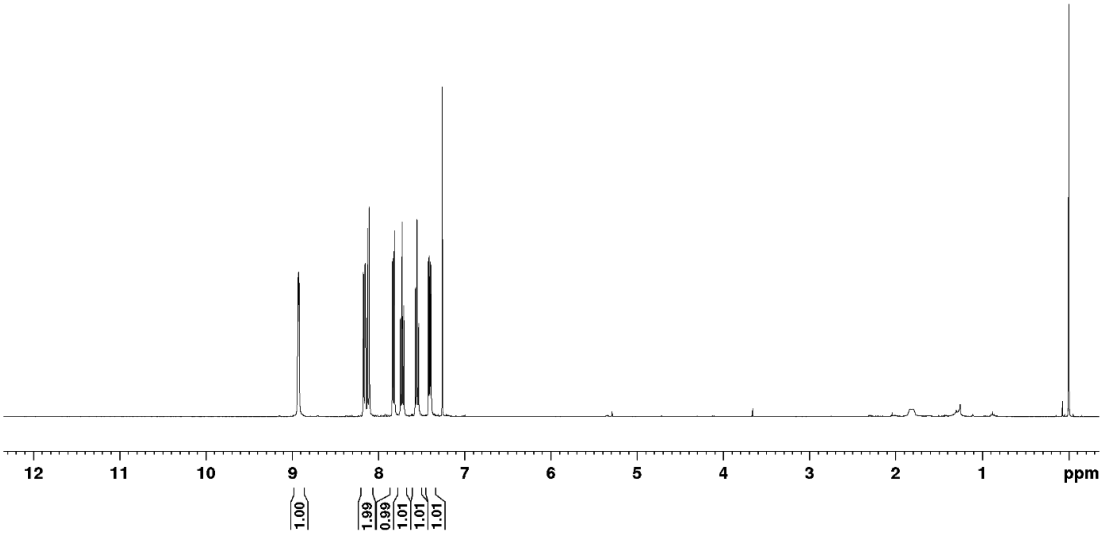

55
9.272
8.531
7.968
7.965
7.818
7.816
7.699
7.663
7.612
1H
8.0
7.9
7.8
7.7
ppm
0.96
0.96
0.96
0.93
0.96
11
10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.02
0.96
0.96
0.96
0.93
0.96


55
152.694
143.170
135.926
130.476
128.858
127.780
127.384
126.619
120.615
13C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

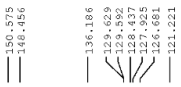
56


8.925
8.106
7.814
7.723
7.553
7.410

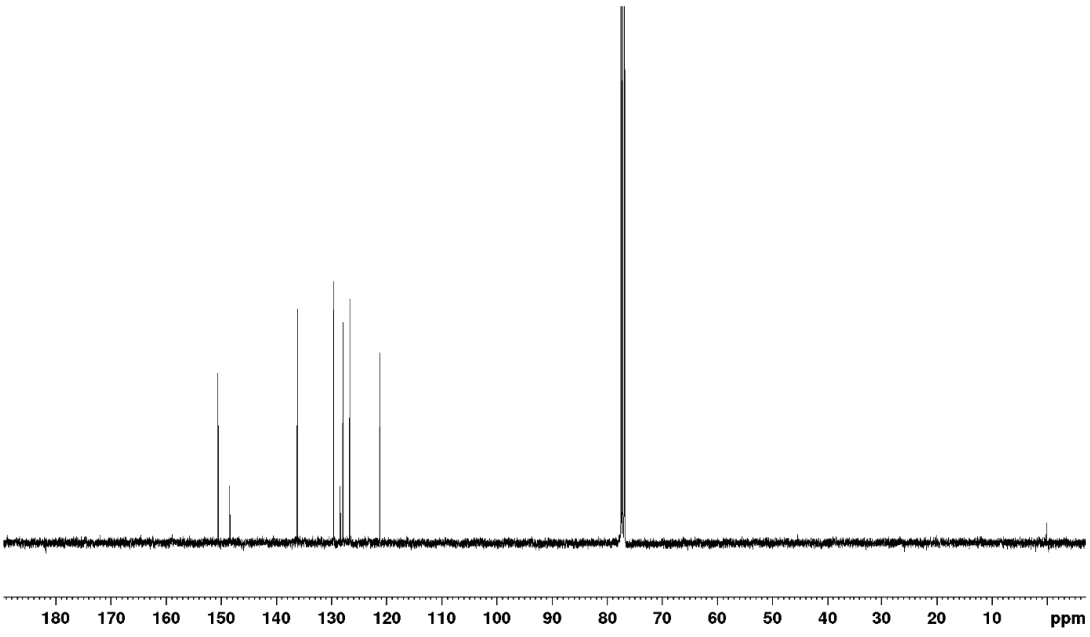
1H

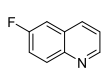

12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.99
0.99
1.01
1.01
1.01

56


150.575
148.456
136.186
129.629
129.592
128.437
127.925
126.681
121.221

13C

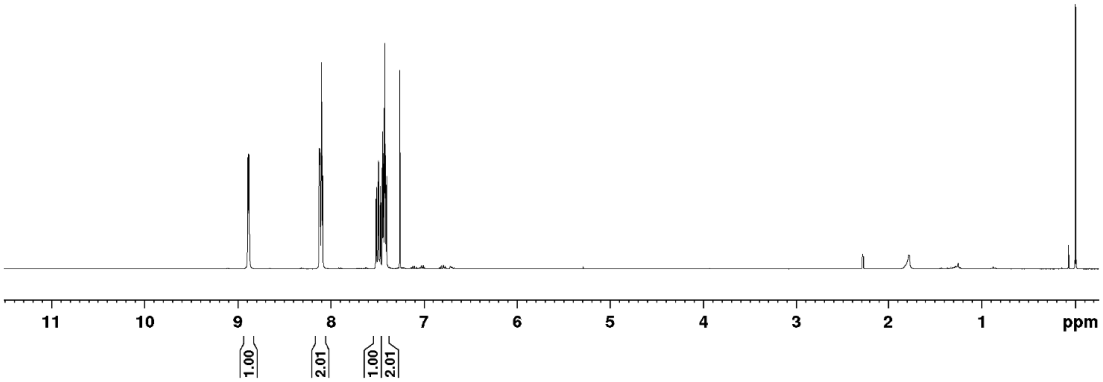

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

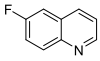


57

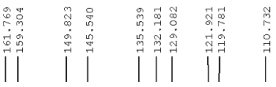

8.882
8.103
7.489
7.424

1H

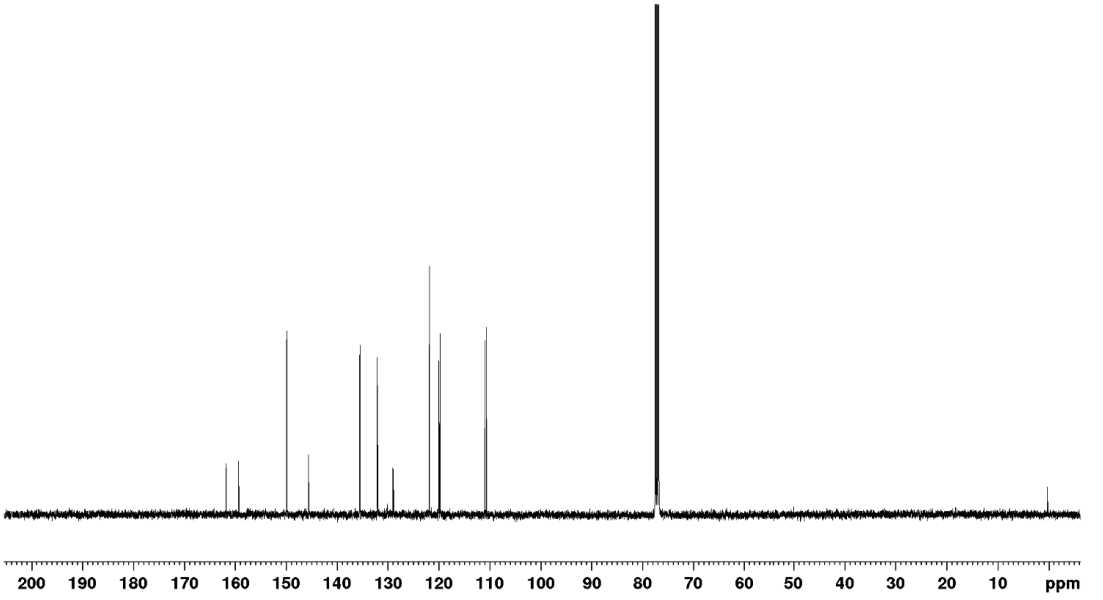

11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.01
1.00
2.01

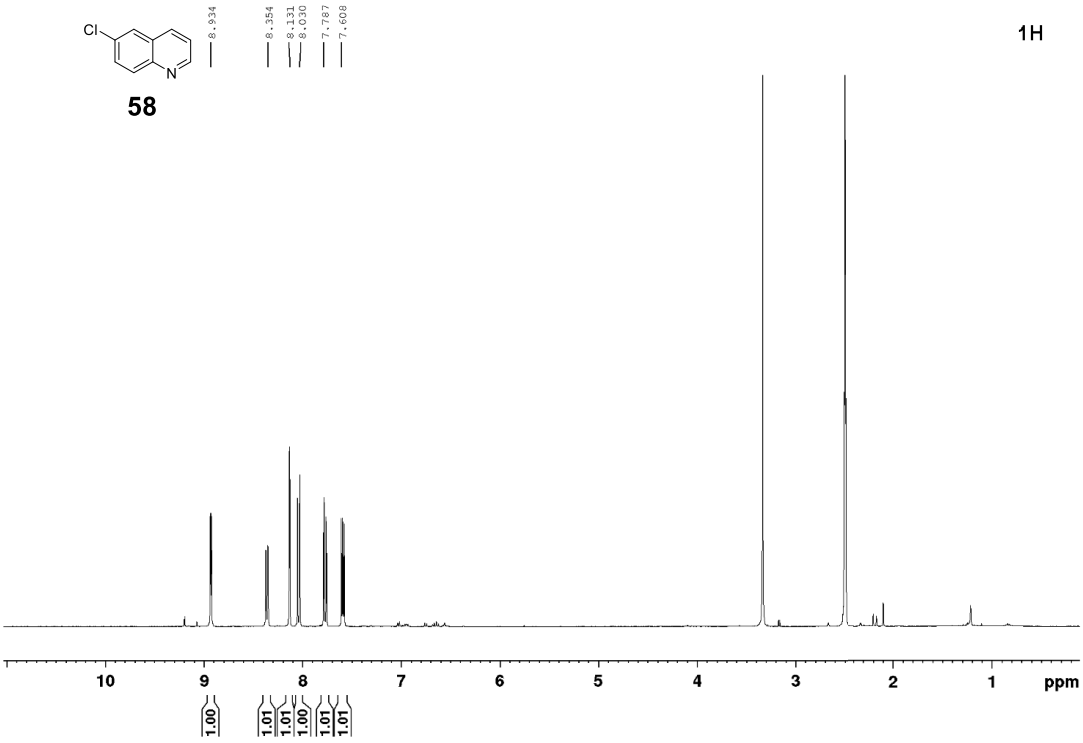


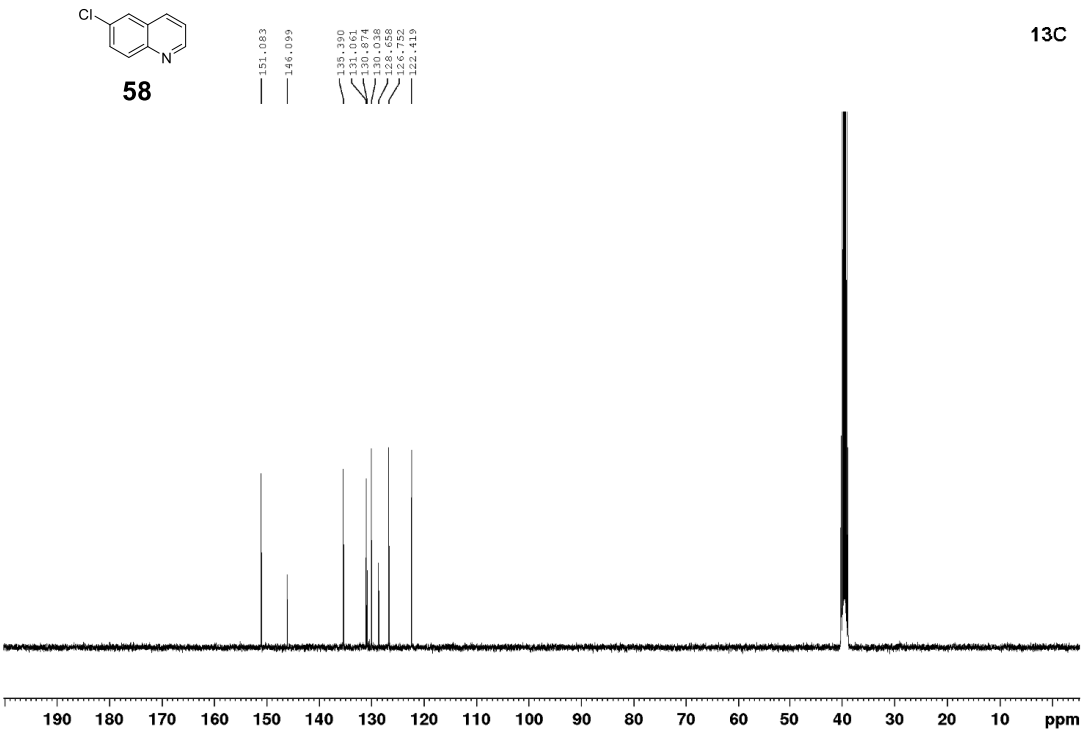
57

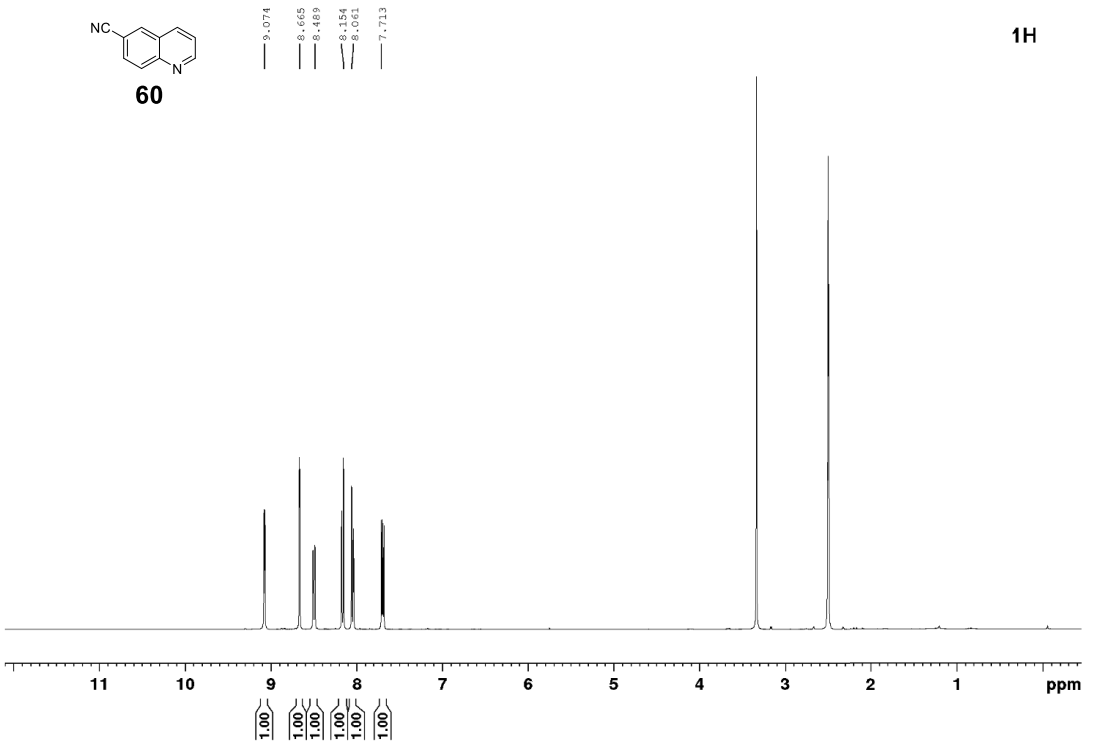

161.769
159.304
149.823
145.540
135.539
132.181
129.082
121.921
119.781
110.732

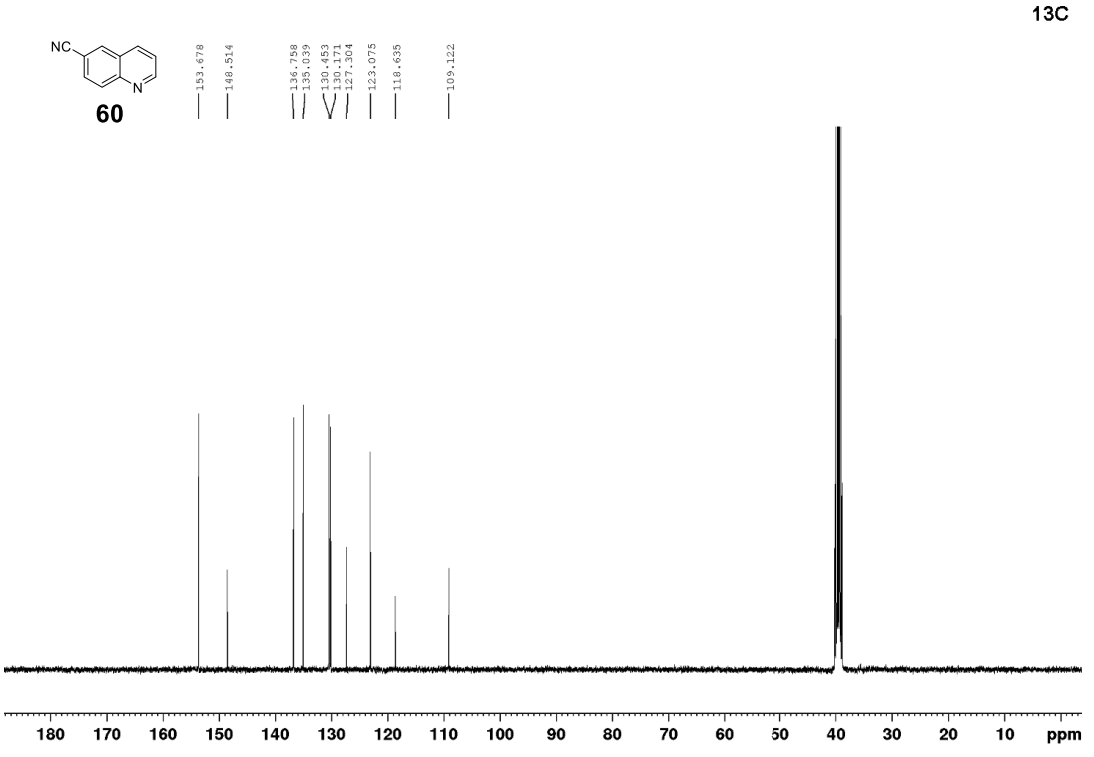
13C

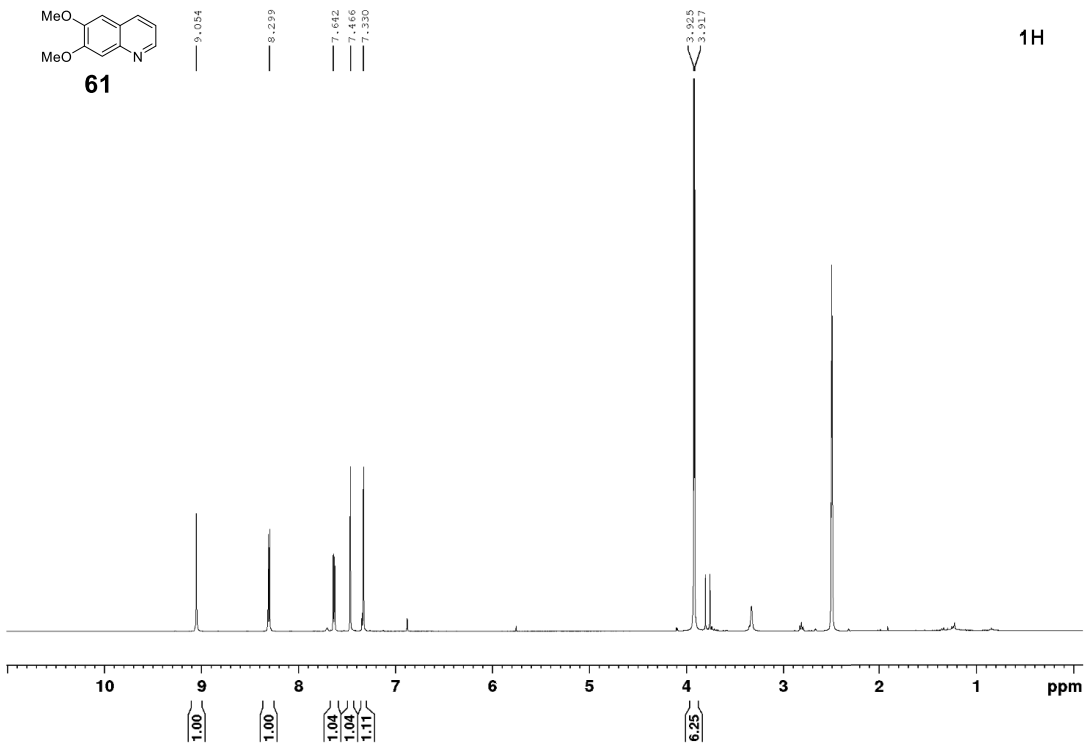

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

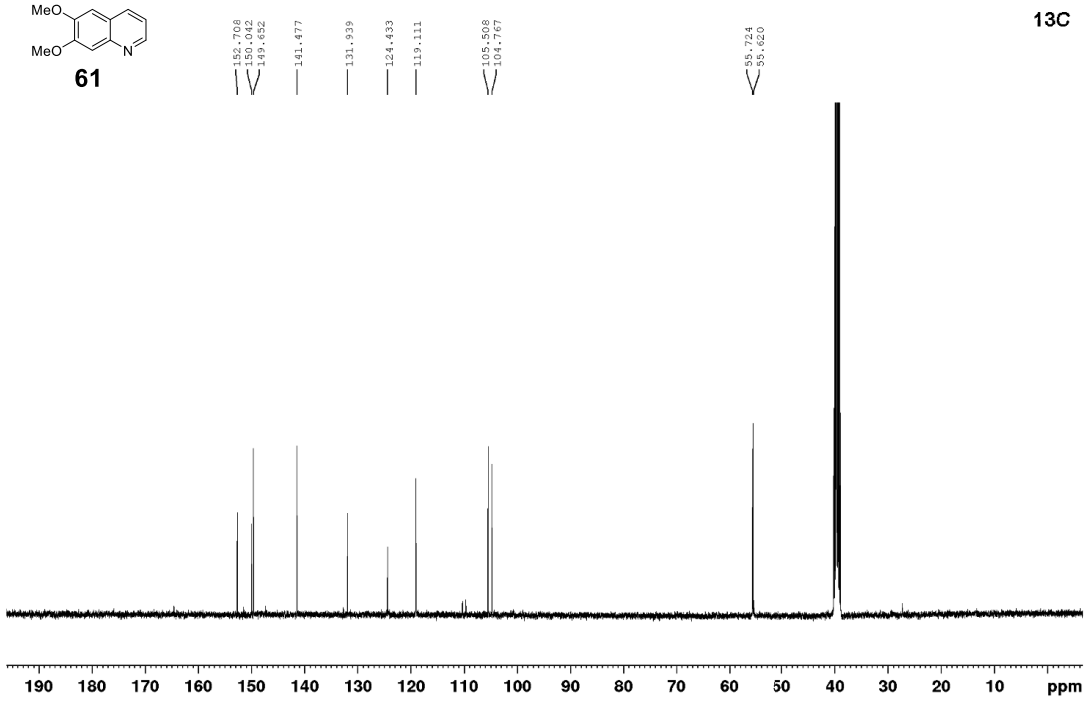

Cl
N
58
8.934
8.354
8.131
8.030
7.787
7.608
1H
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
1.01
1.00
1.01
1.01

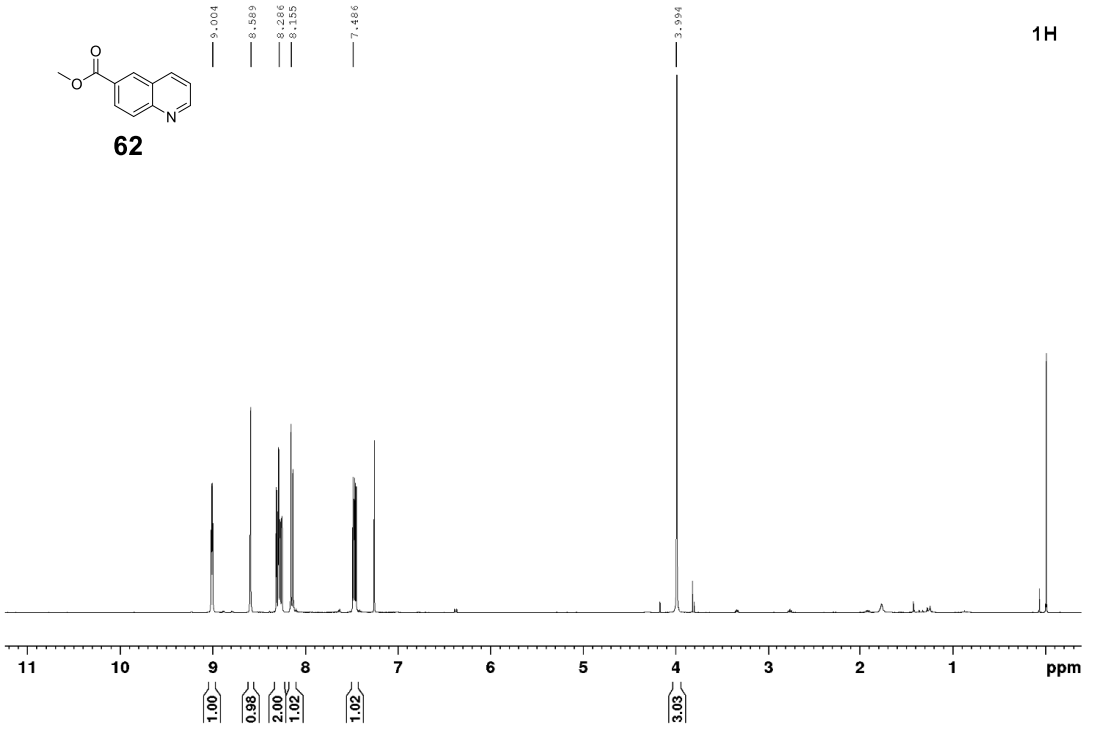

Cl
N
58
151.083
146.099
135.390
131.061
130.874
130.038
128.658
126.752
122.419
13C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

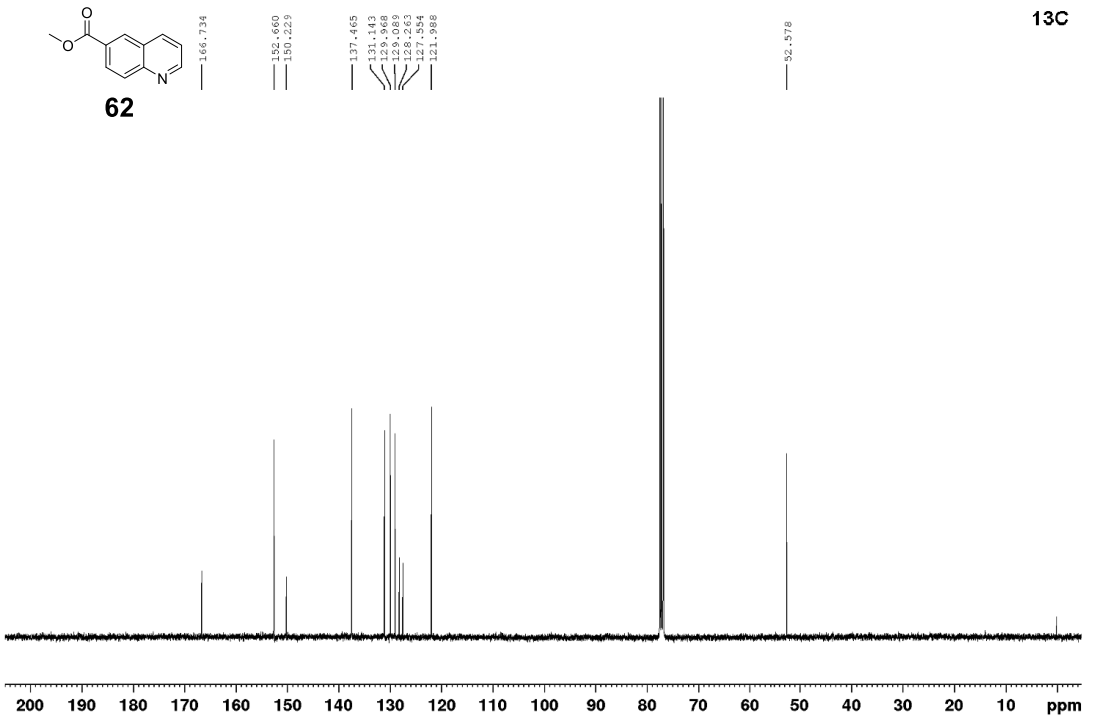

NC
N
60
9.074
8.665
8.489
8.154
8.061
7.713
1H
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.00
1.00
1.00
1.00

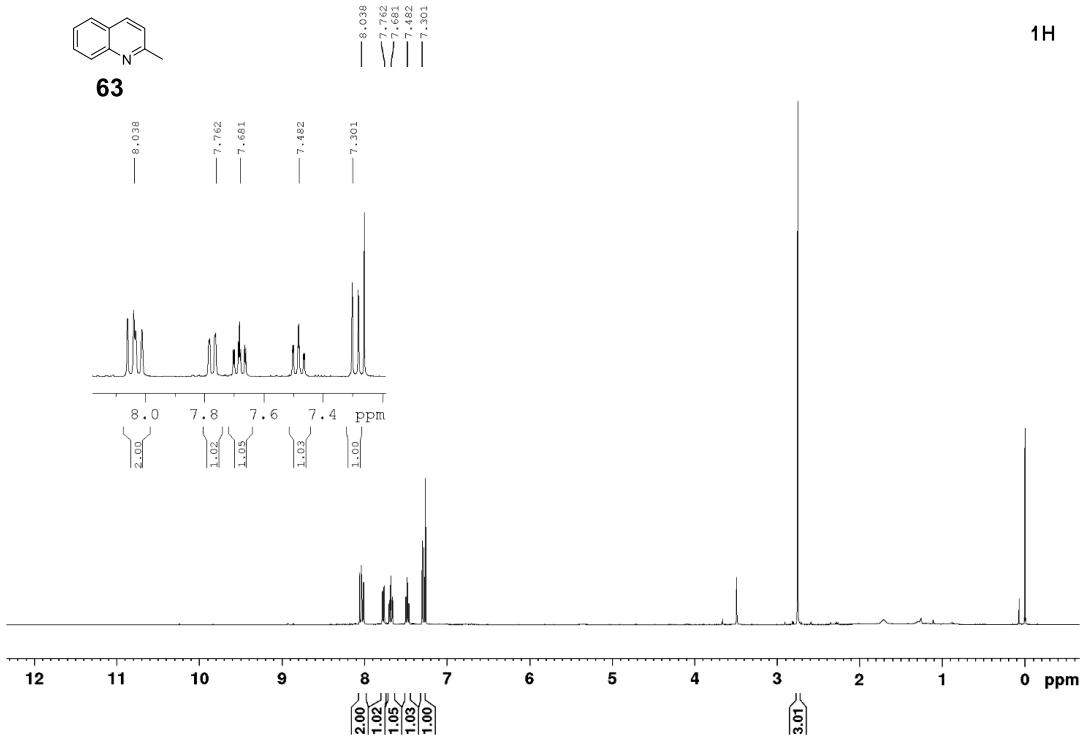

NC
N
60
153.678
148.514
136.758
133.039
130.453
130.171
127.364
123.075
118.635
109.122
13C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

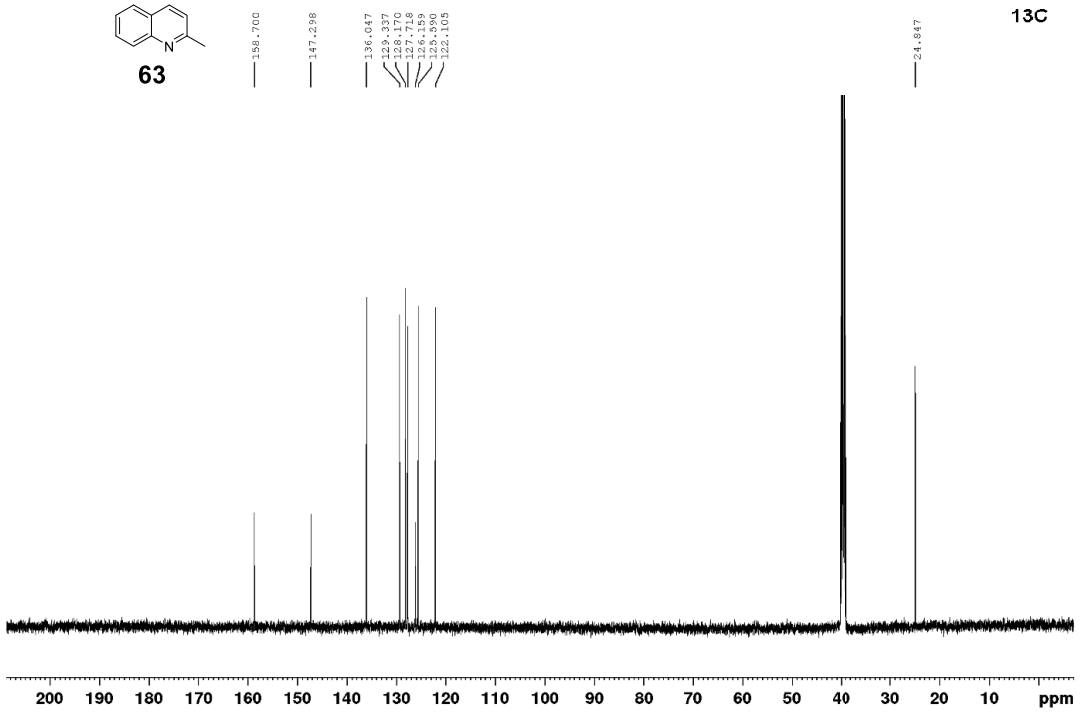

MeO
MeO
N
61
9.054
8.299
7.642
7.466
7.330
3.925
3.917
1H
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.00
1.04
1.04
1.11
6.25

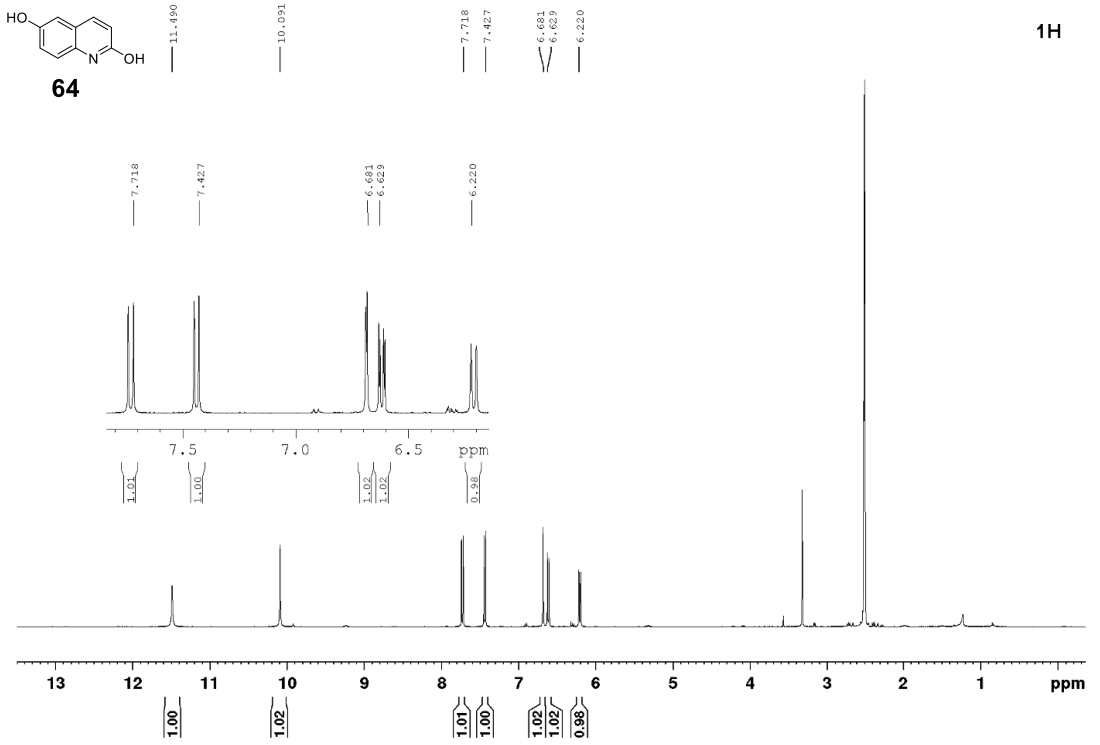

MeO
MeO
N
61
152.708
150.042
149.652
141.477
131.939
124.433
119.111
105.508
104.767
55.724
55.620
13C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

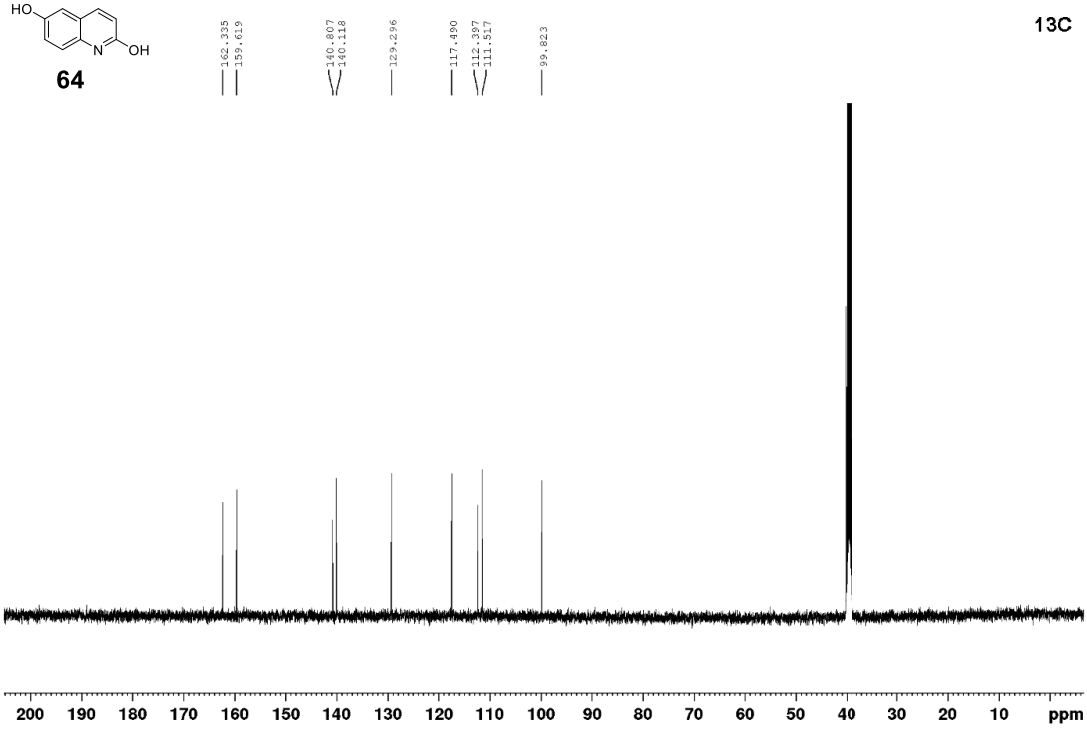

9.004
8.589
8.286
8.155
7.486
3.994
1H
62
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.98
2.00
1.02
1.02
3.03


166.734
152.660
150.229
137.465
131.143
129.968
129.089
128.263
127.594
121.988
52.578
13C
62
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


63
8.038
7.762
7.681
7.482
7.301
1H
8.0
7.8
7.6
7.4
ppm
2.00
1.02
1.05
1.03
1.00
3.01
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


63
158.700
147.298
136.047
129.337
128.170
127.718
126.159
125.590
122.105
24.847
13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HO
N
OH
64
11.490
10.091
7.718
7.427
6.681
6.629
6.220
1H
7.5
7.0
6.5
ppm
1.01
1.00
1.02
1.02
0.98
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.01
1.00
1.02
1.02
0.98

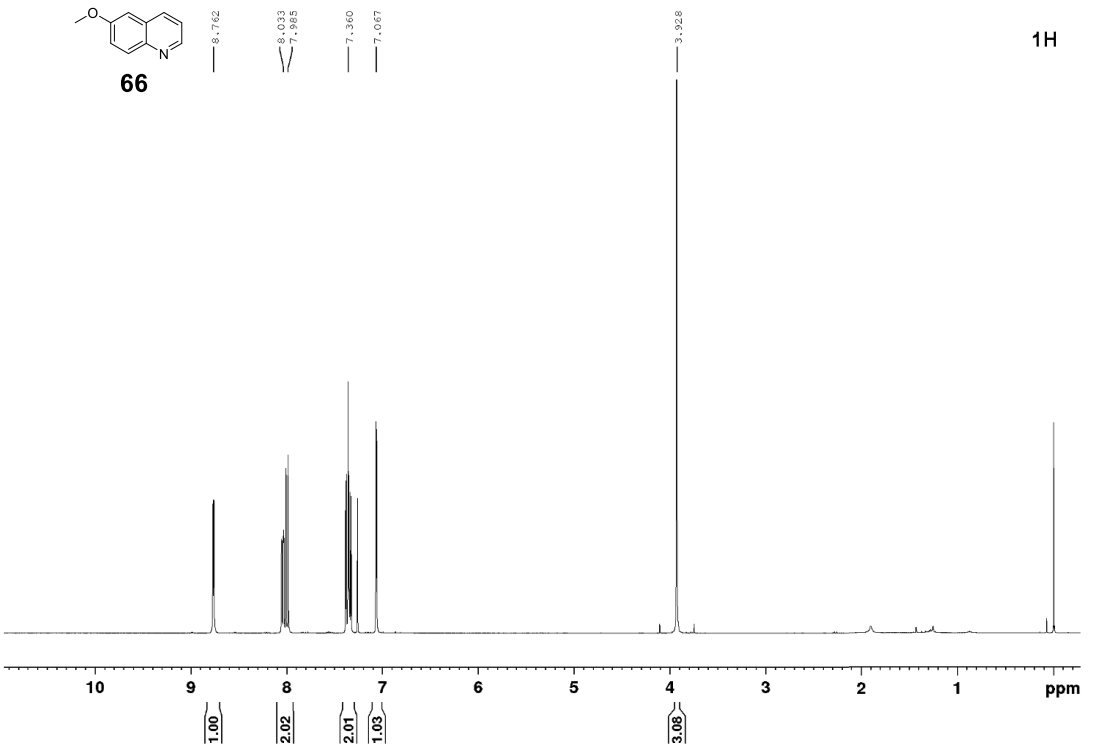

HO
N
OH
64
162.335
159.619
140.807
140.118
129.296
117.490
112.397
111.517
99.823
13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

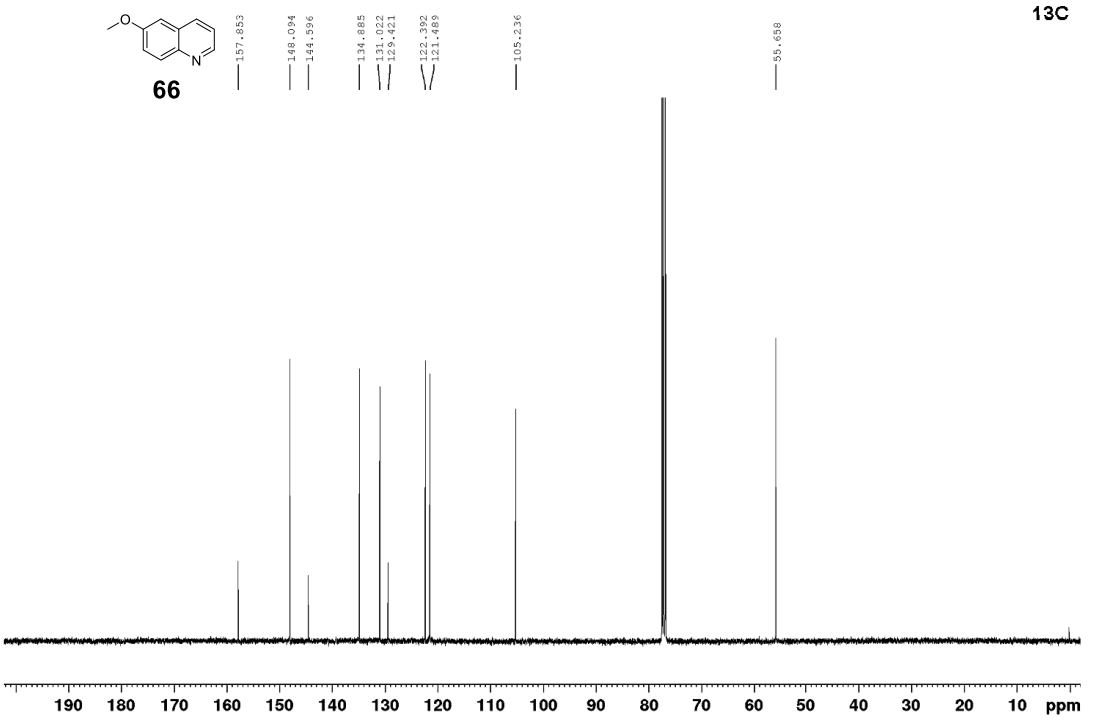
65

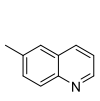
8.861
8.114
7.806
1H
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.00
1.97
2.02

65

145.143
143.223
130.234
129.689
13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


66
8.762
8.033
7.985
7.360
7.067
3.928
1H
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.02
2.01
1.03
3.08


66
157.853
148.094
144.596
134.885
131.022
129.421
122.392
121.489
105.236
55.658
13C
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

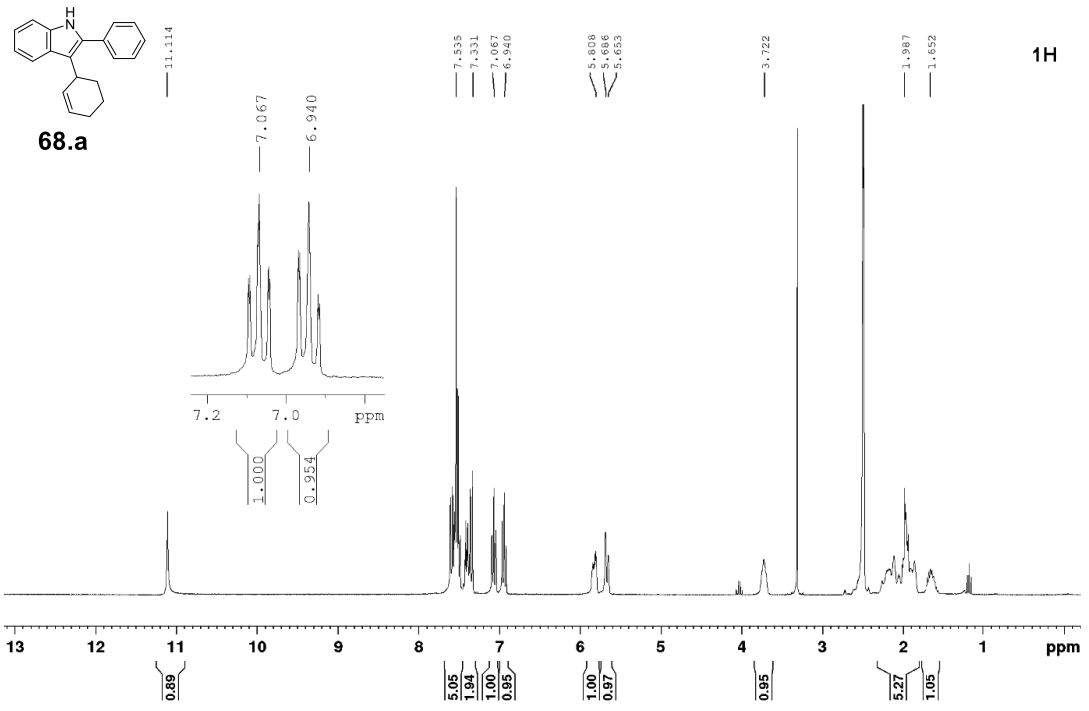


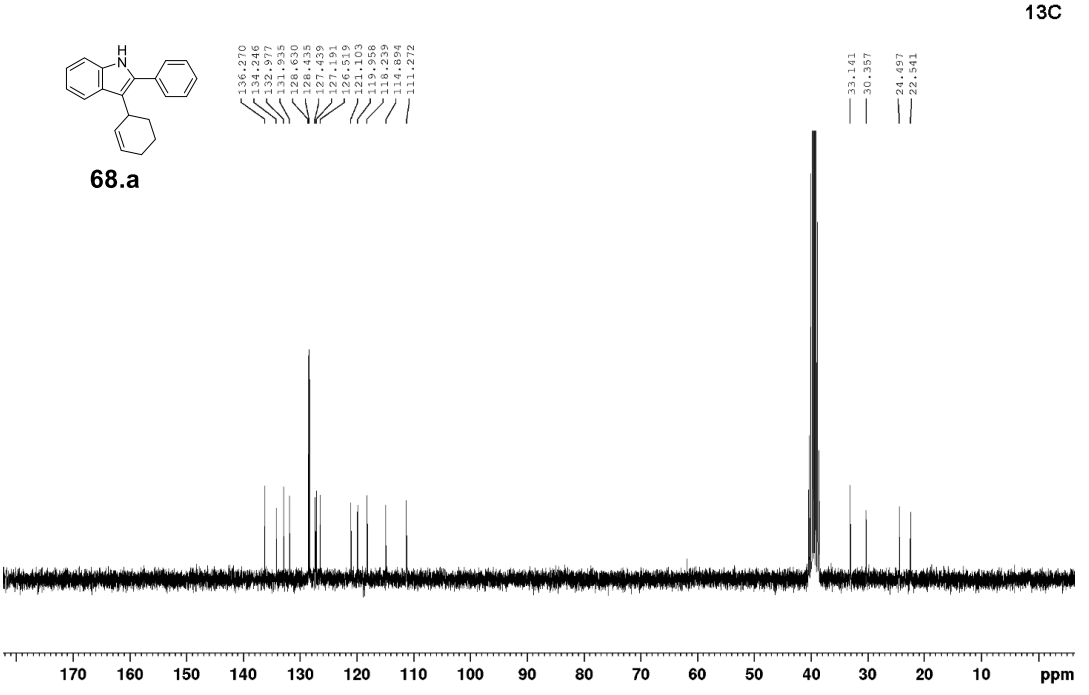
67

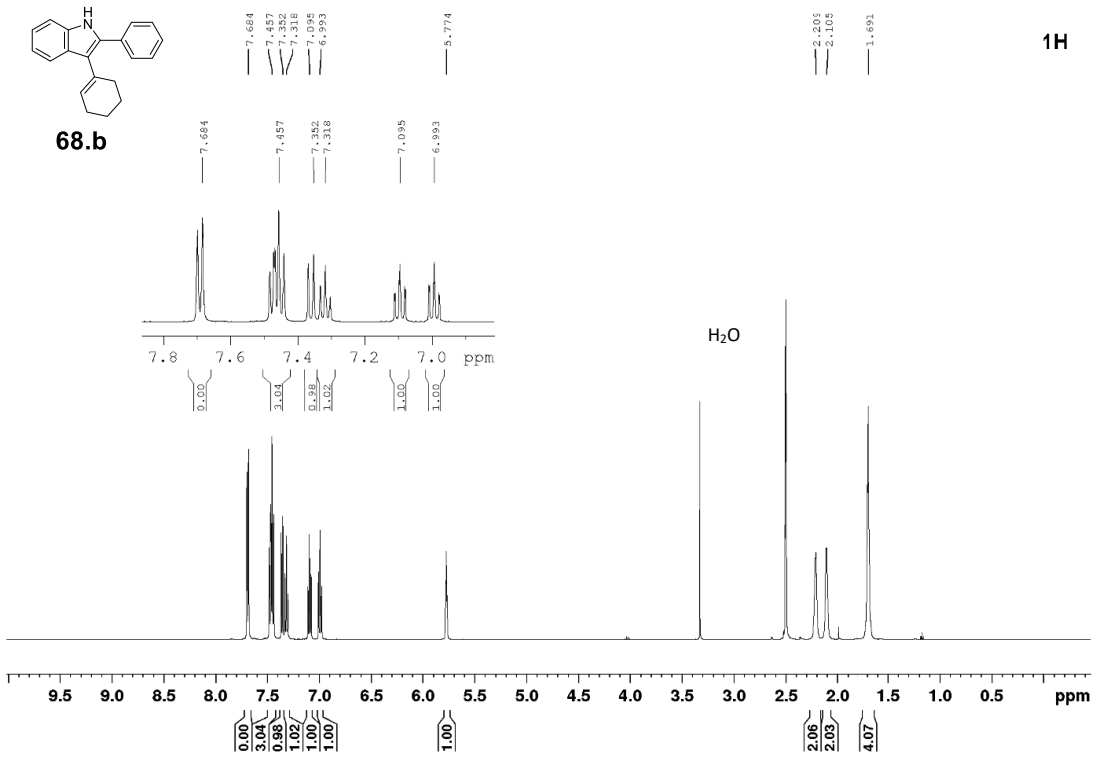
8.642
8.052
7.989
7.573
7.368
1H
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.99
1.01
2.00
1.03

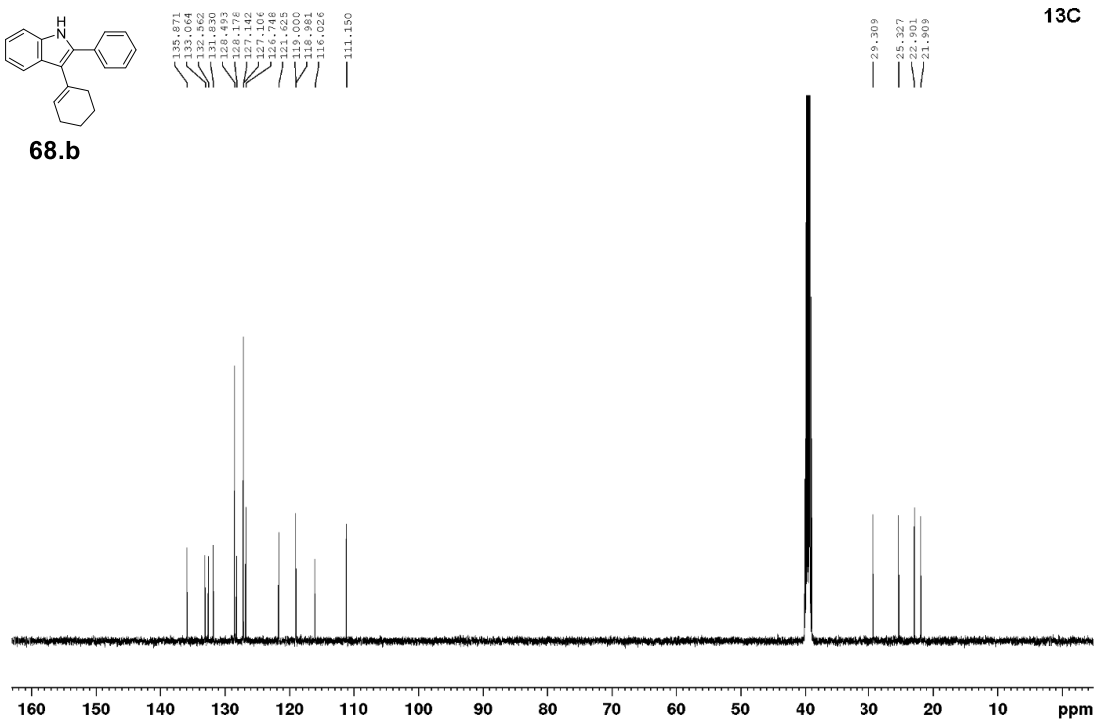
67

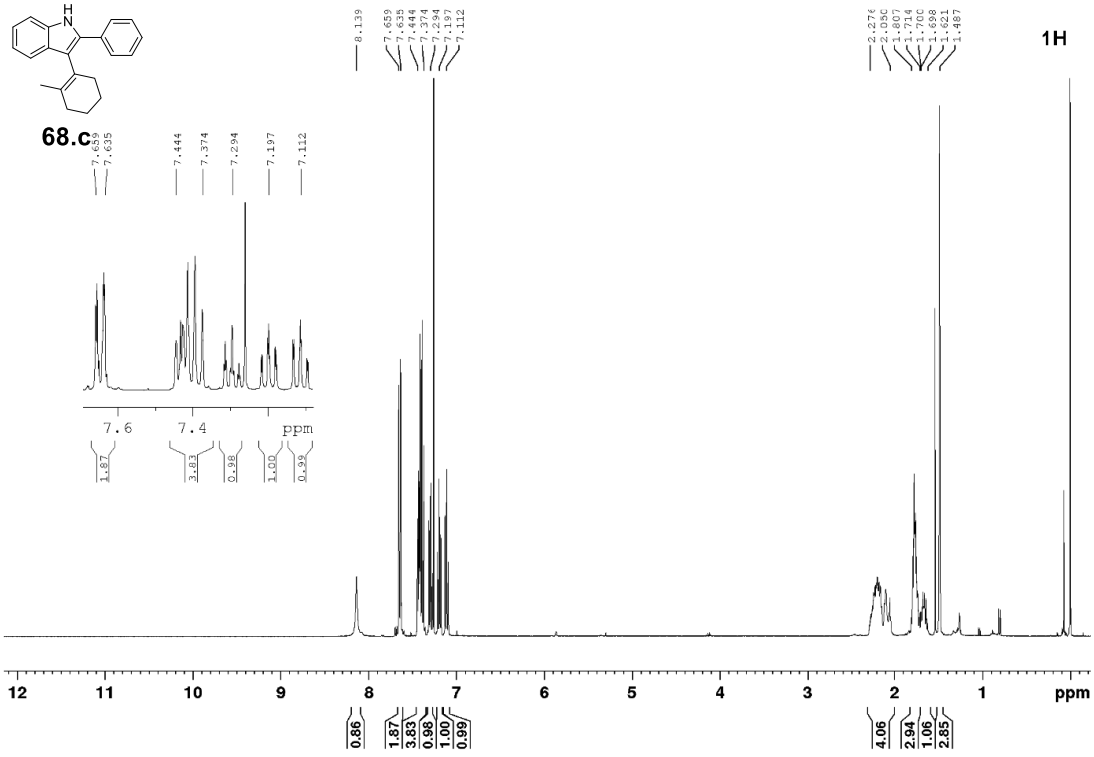
149.678
147.049
136.520
135.493
131.876
129.257
128.455
126.720
121.202
21.710
13C
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

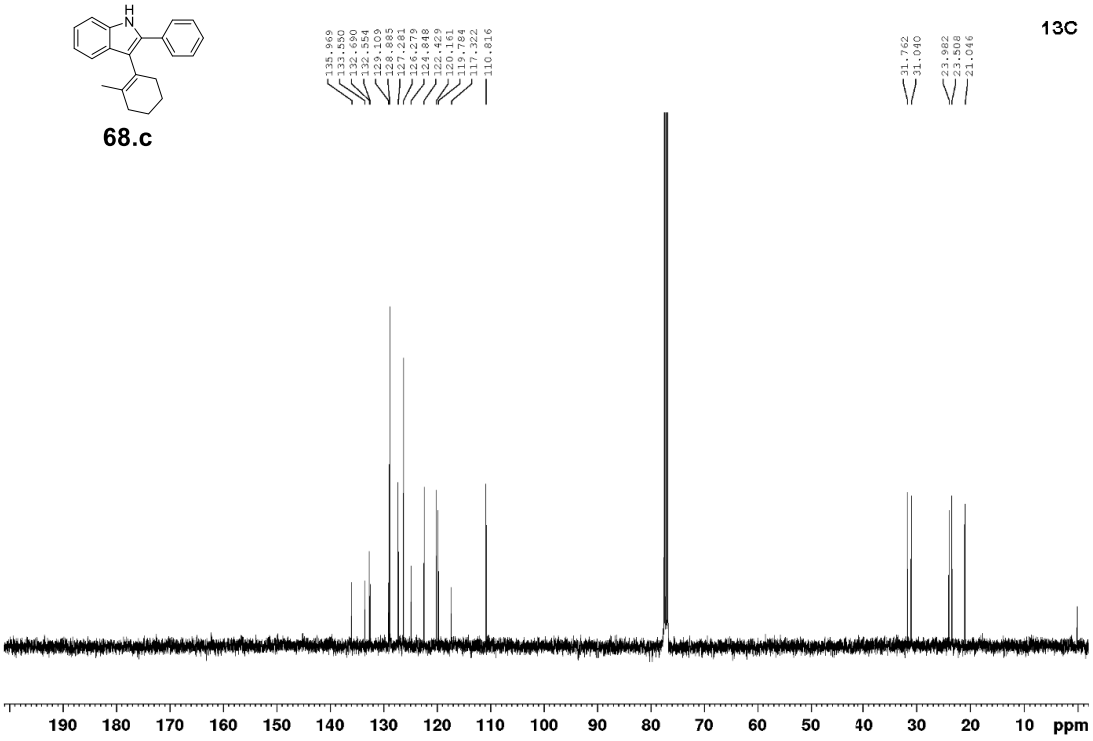

68.a
11.114
7.535
7.331
7.067
6.940
5.808
5.686
5.653
3.722
1.987
1.652
1H
7.067
6.940
7.2
7.0
ppm
1.000
0.954
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.89
5.05
1.94
1.00
0.95
1.00
0.97
0.95
5.27
1.05

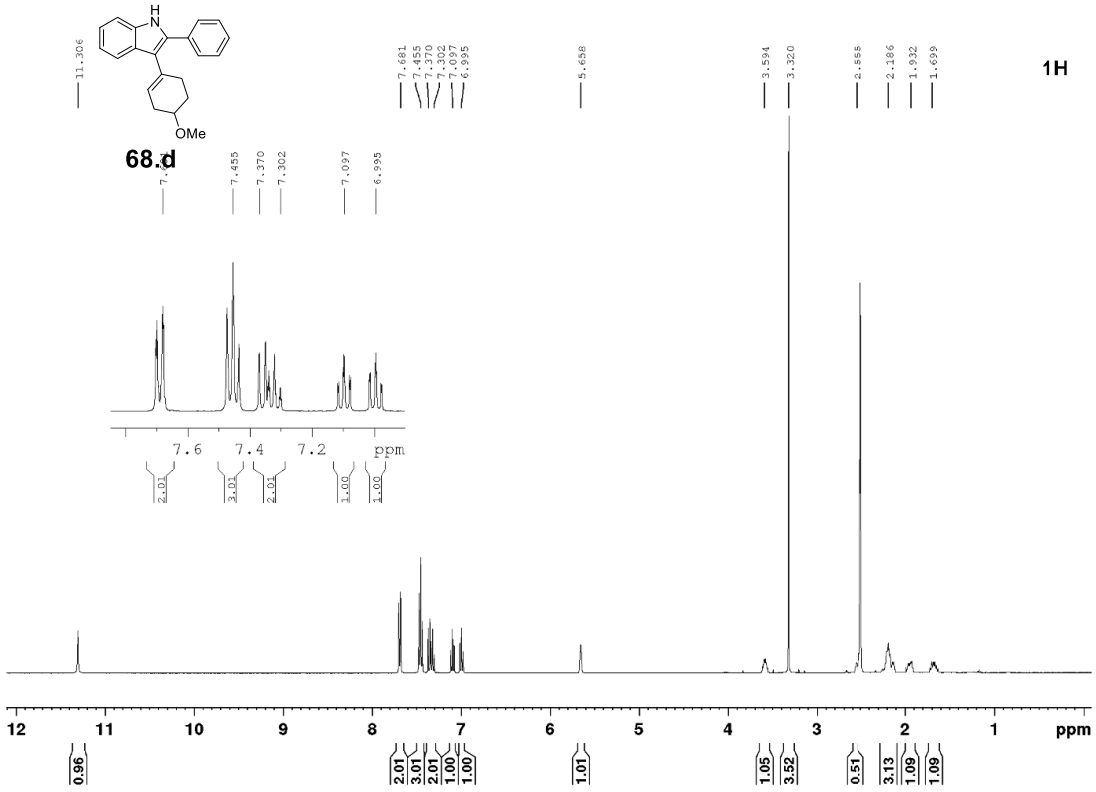

13C
68.a
136.270
134.246
132.977
131.935
128.630
128.435
127.439
127.191
126.519
121.103
119.958
118.239
114.894
111.272
33.141
30.357
24.497
22.541
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

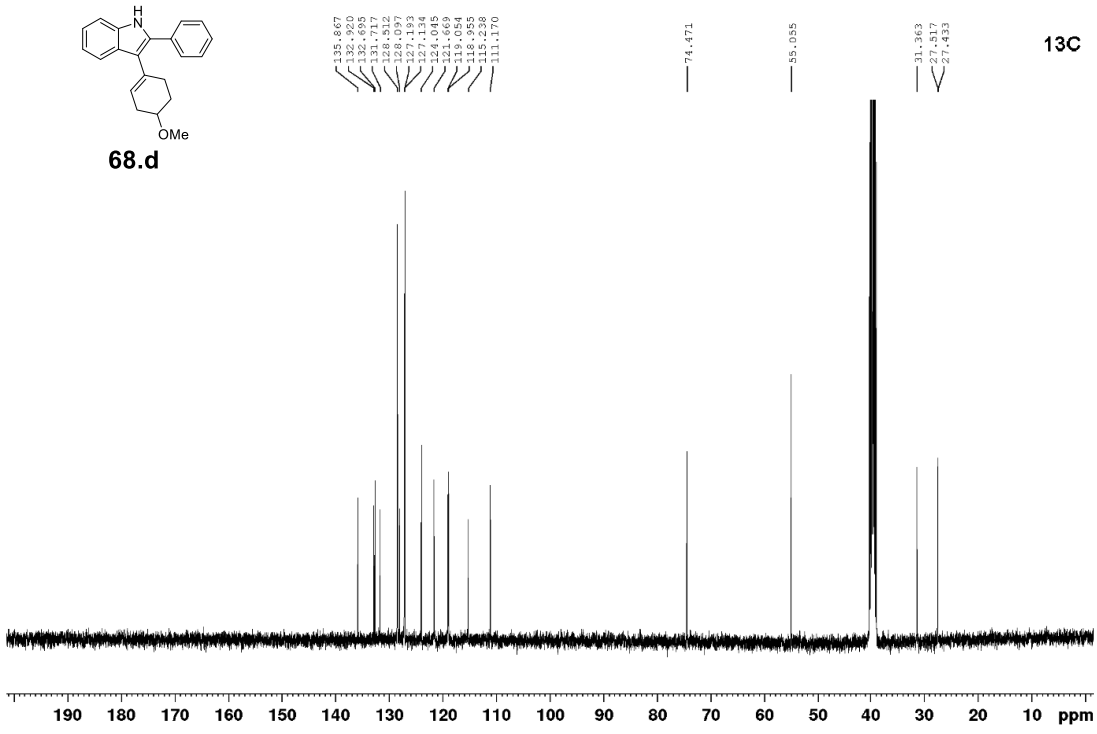

68.b
1H
7.684
7.457
7.352
7.318
7.095
6.993
5.774
2.203
2.105
1.691
H2O
ppm

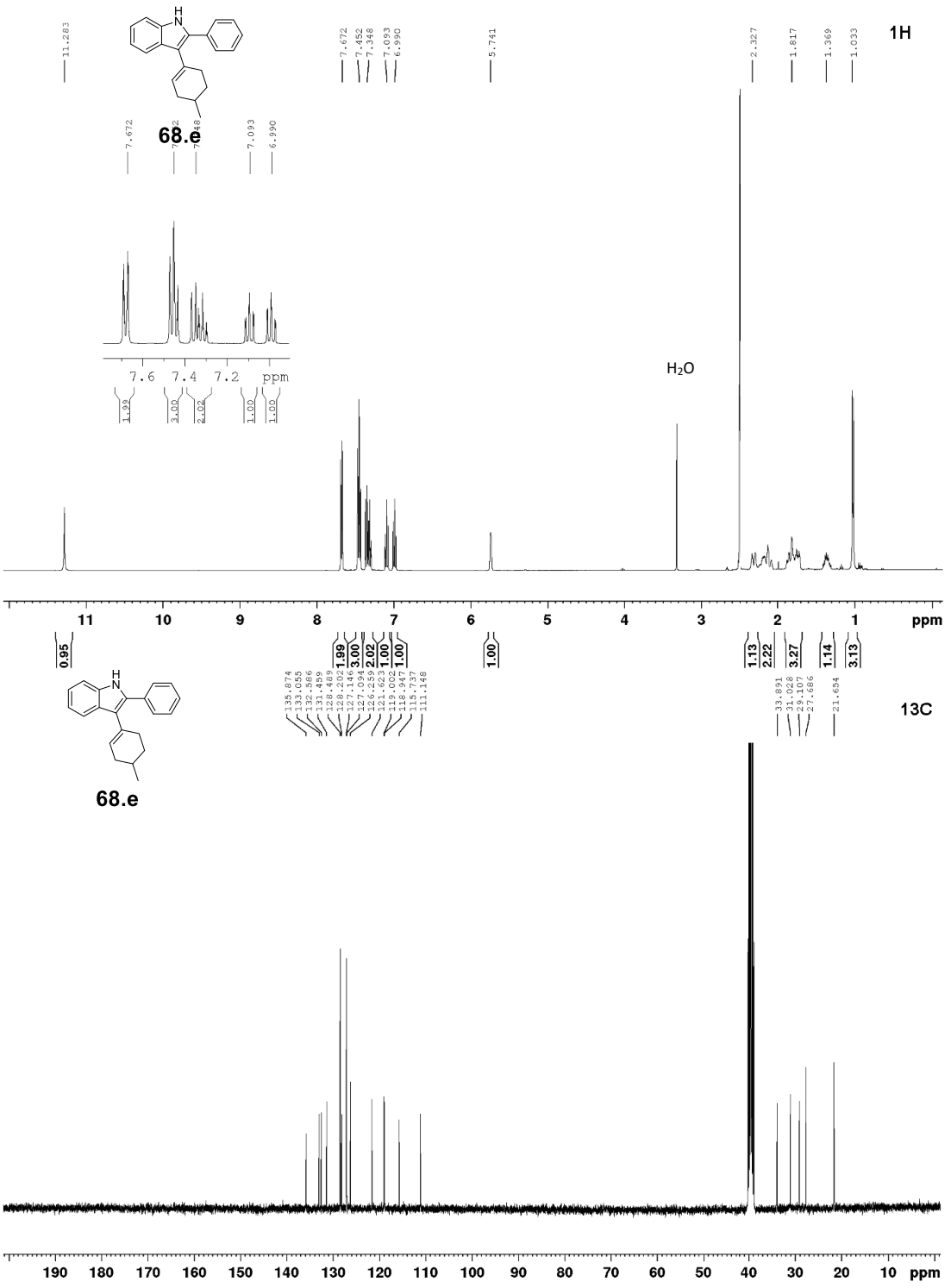

68.b
13C
135.871
133.064
132.562
131.830
128.493
128.178
127.142
127.106
126.748
121.625
119.000
118.981
116.026
111.150
29.309
25.327
22.901
21.909
ppm

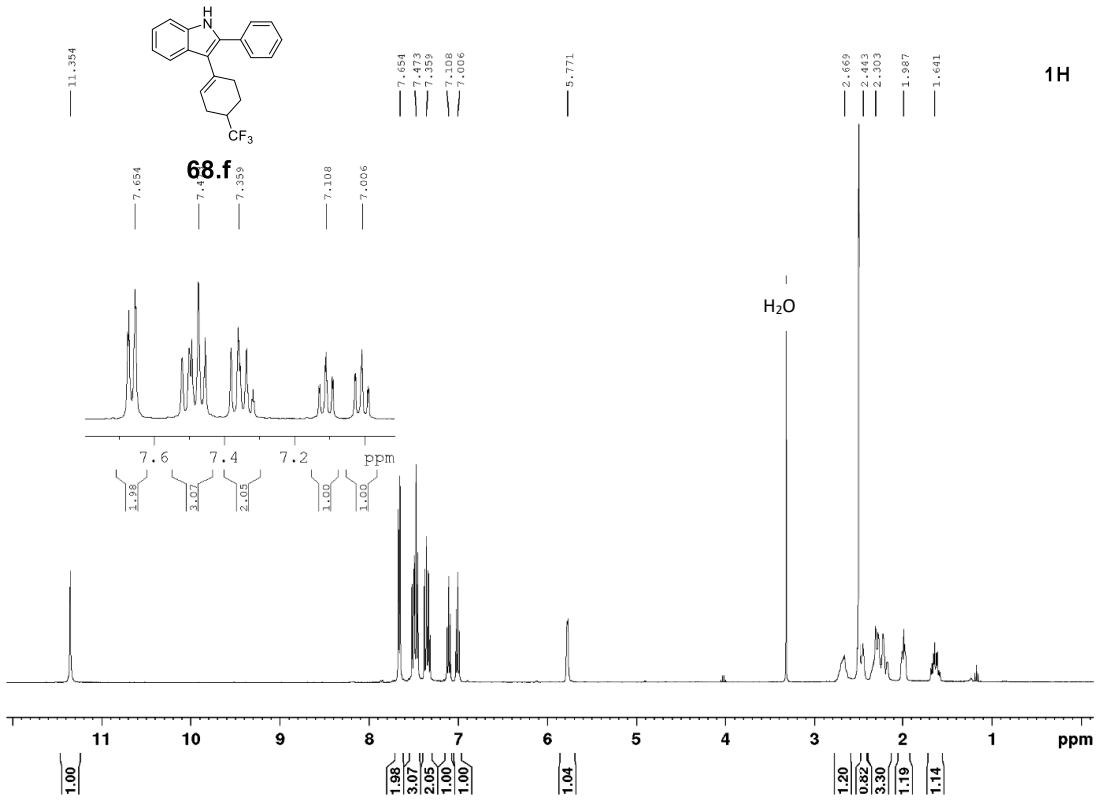

68.c
1H
8.139
7.659
7.635
7.444
7.374
7.294
7.197
7.112
2.276
2.050
1.807
1.774
1.706
1.698
1.621
1.487
7.6
7.4
ppm
1.87
3.83
0.98
1.00
0.99
4.06
2.94
1.06
2.85
12
11
10
9
8
7
6
5
4
3
2
1
ppm

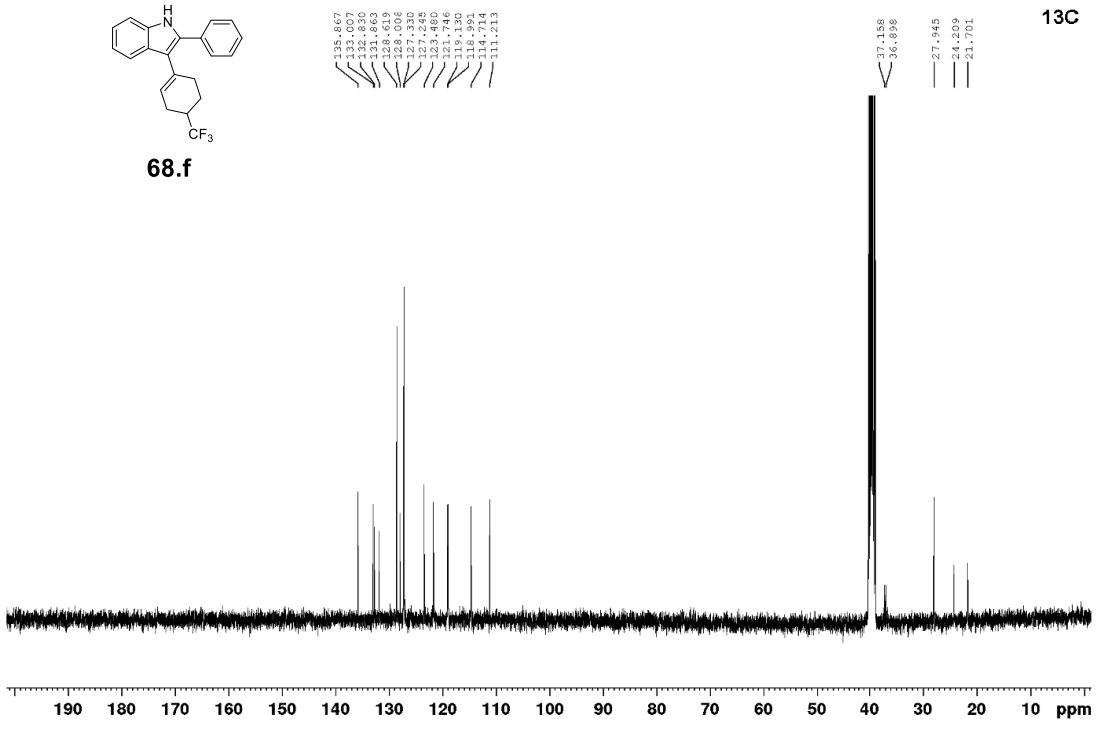

68.c
13C
135.969
133.550
132.690
132.554
129.109
128.885
127.281
126.279
124.848
122.429
120.161
119.784
117.322
110.816
31.762
31.040
23.982
23.508
21.046
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

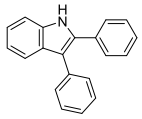

68.d
1H
11.306
7.681
7.455
7.370
7.302
7.097
6.995
5.658
3.594
3.320
2.555
2.186
1.932
1.699
7.6
7.4
7.2
ppm
2.01
3.01
2.01
1.00
1.00
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.96
2.01
3.01
2.01
1.00
1.00
1.01
1.05
3.52
0.51
3.13
1.09
1.09


68.d
13C
135.867
132.920
132.695
131.717
128.512
128.097
127.133
127.134
124.045
121.669
119.054
118.955
115.238
111.170
74.471
55.055
31.363
27.517
27.433
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


1H
68.e
H2O
13C
68.e
ppm

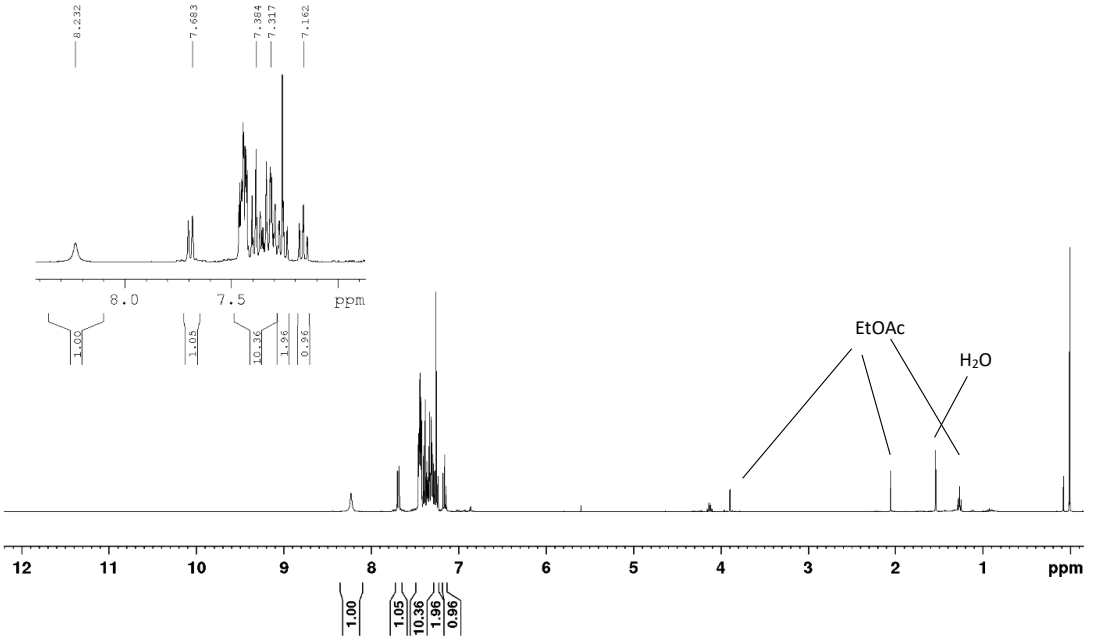

68.f
1H
11.354
7.654
7.473
7.359
7.108
7.006
5.771
2.669
2.443
2.303
1.987
1.641
H2O
7.6
7.4
7.2
ppm
1.98
3.07
2.05
1.00
1.00
1.00
1.04
1.20
0.82
3.30
1.19
1.14
11
10
9
8
7
6
5
4
3
2
1
ppm


68.f
13C
135.867
133.007
132.830
131.863
128.619
128.096
127.730
127.245
123.480
121.746
119.130
118.991
114.714
111.213
37.158
36.898
27.945
24.209
21.701
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

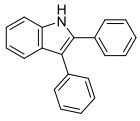


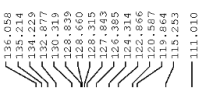
69.a = 69.b

1H

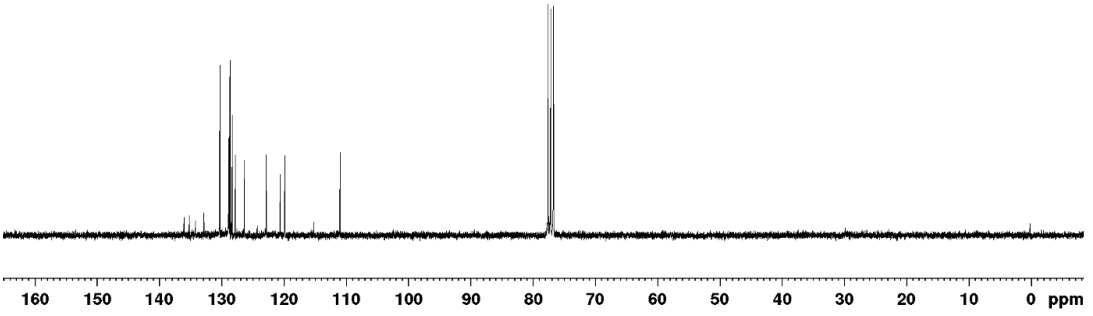


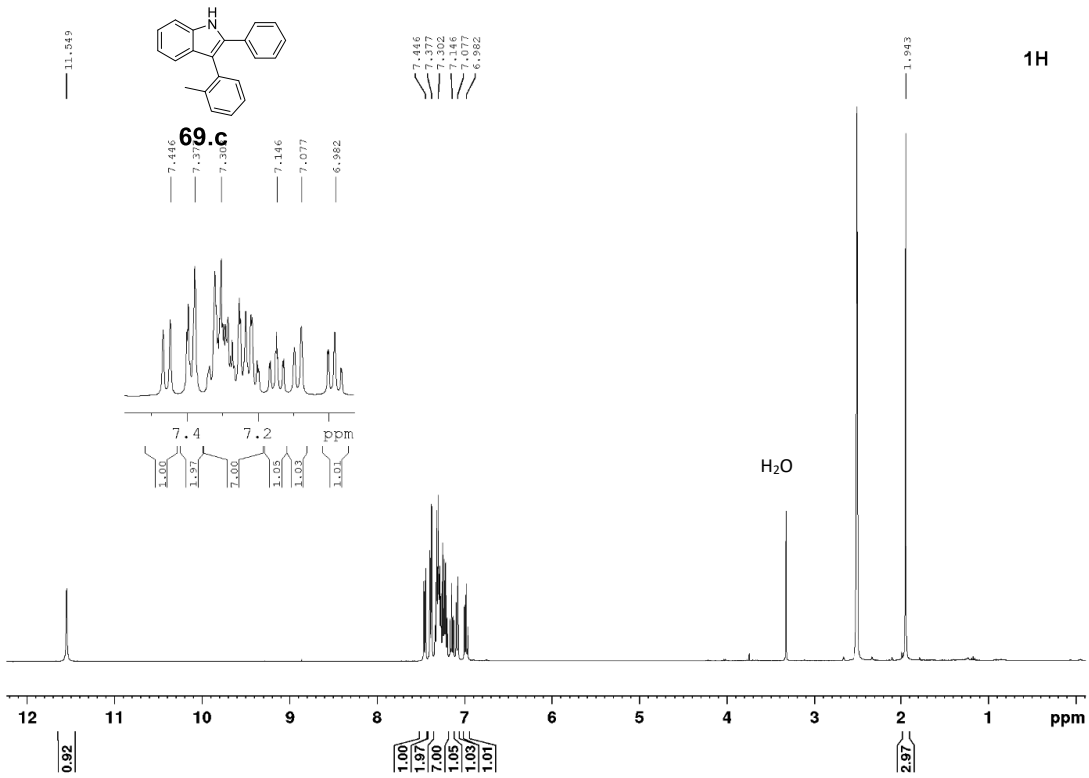
13C

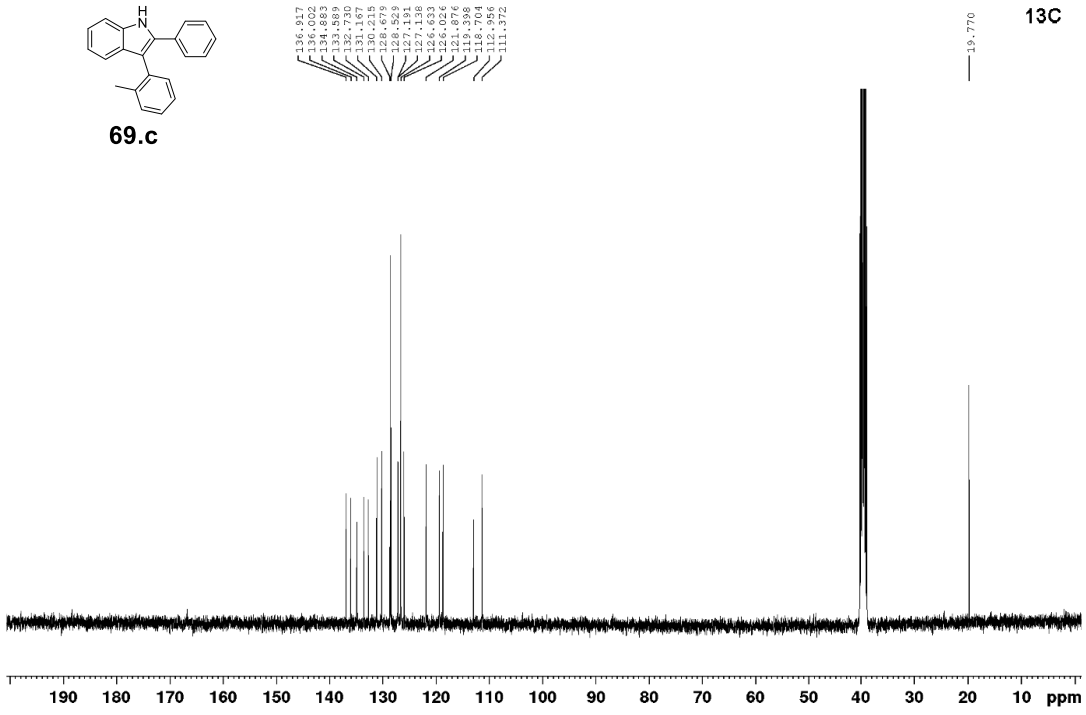


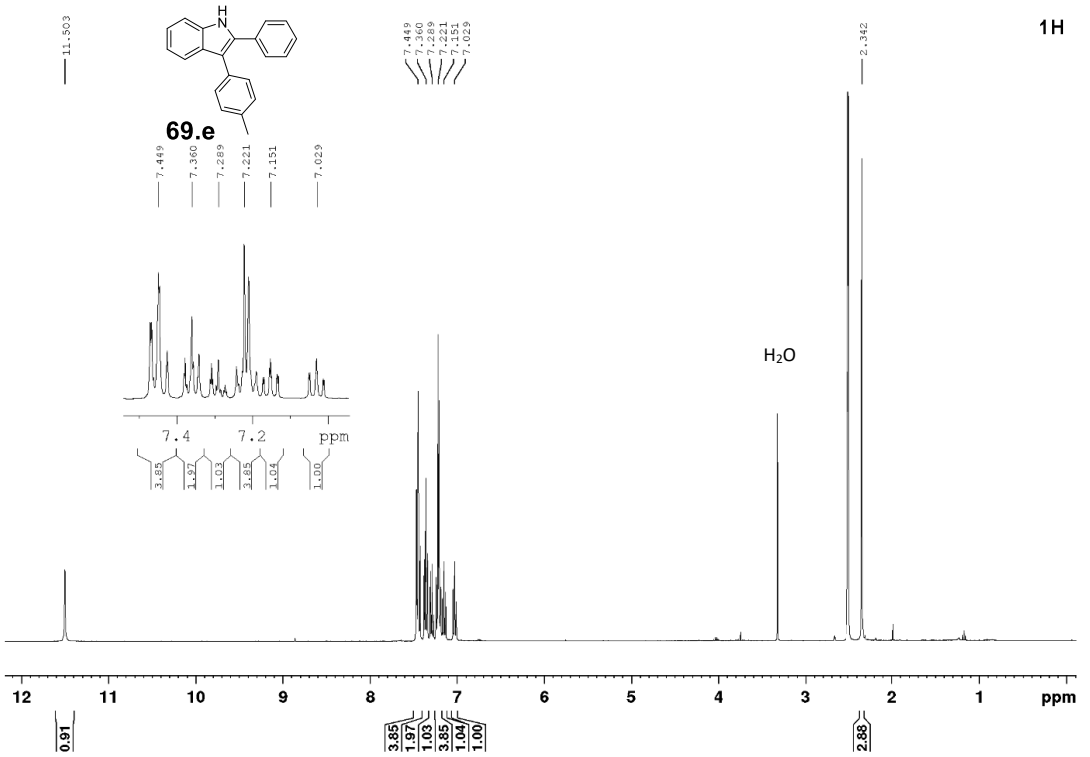


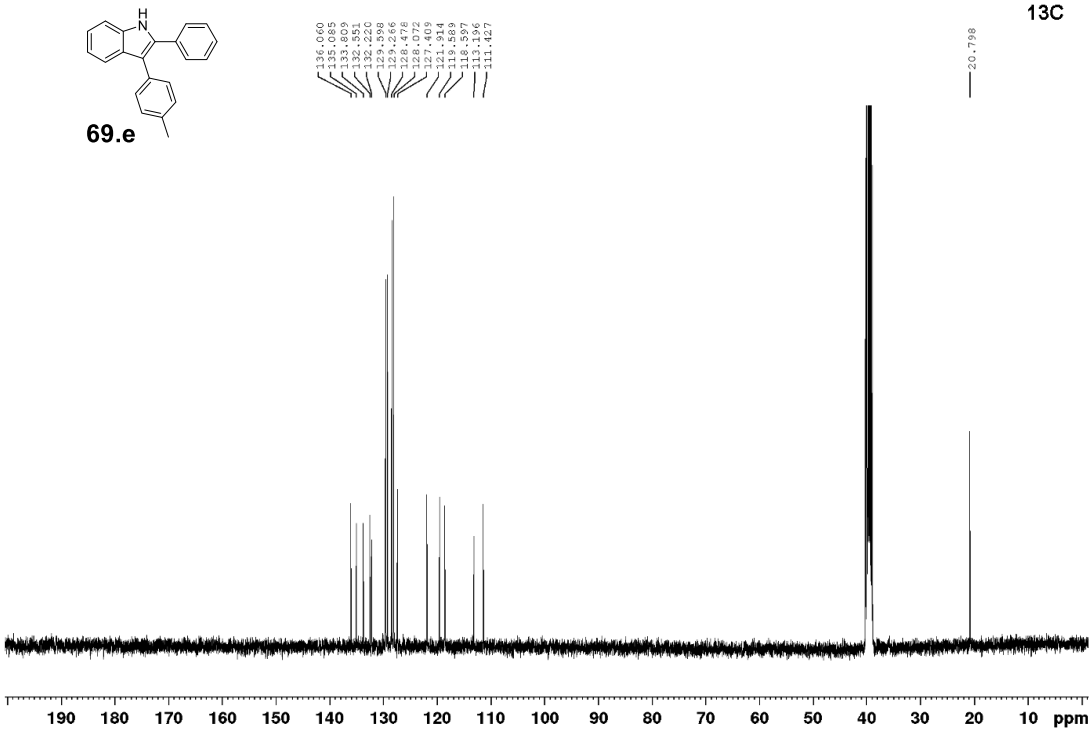
69.a = 69.b

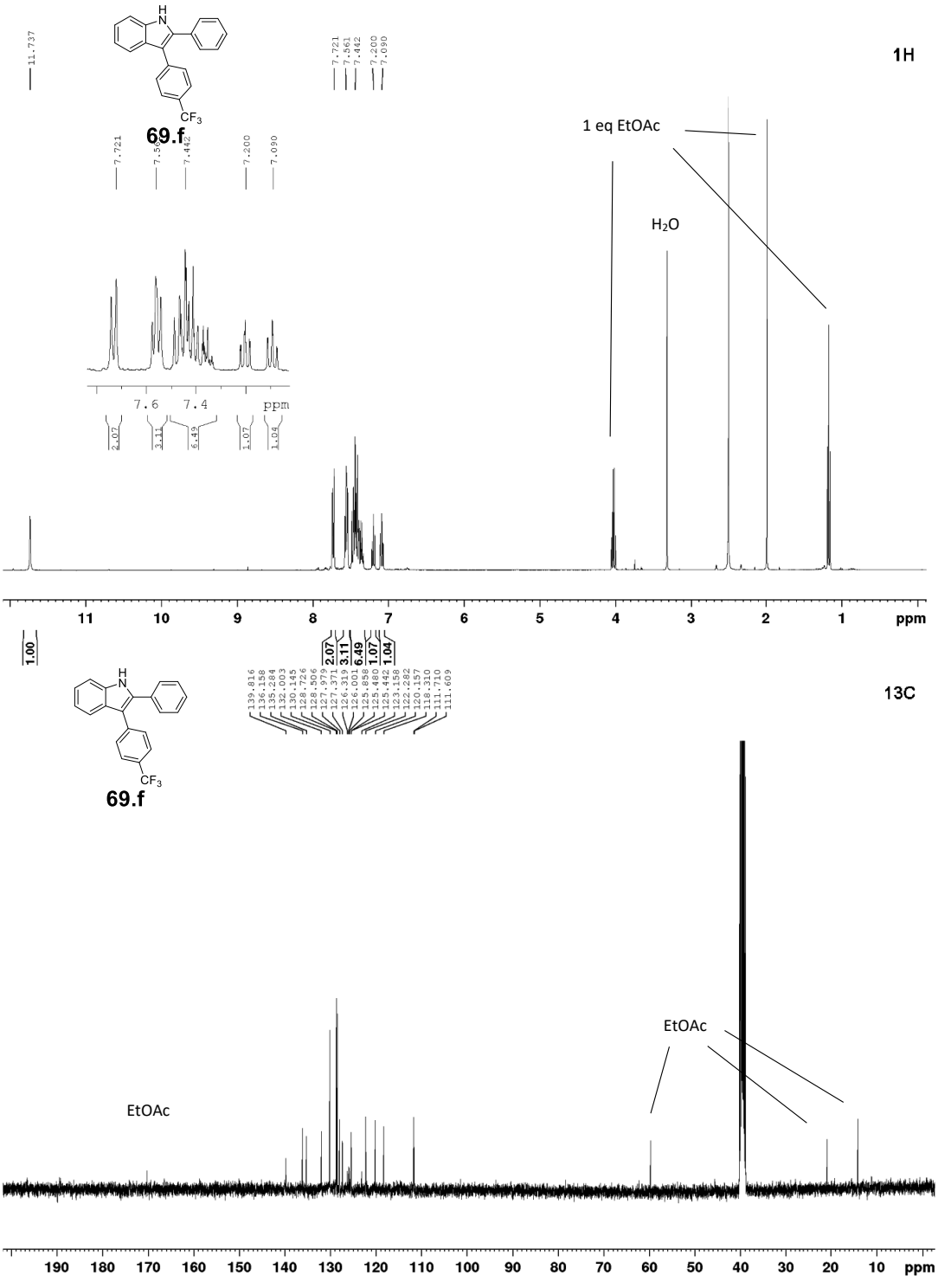


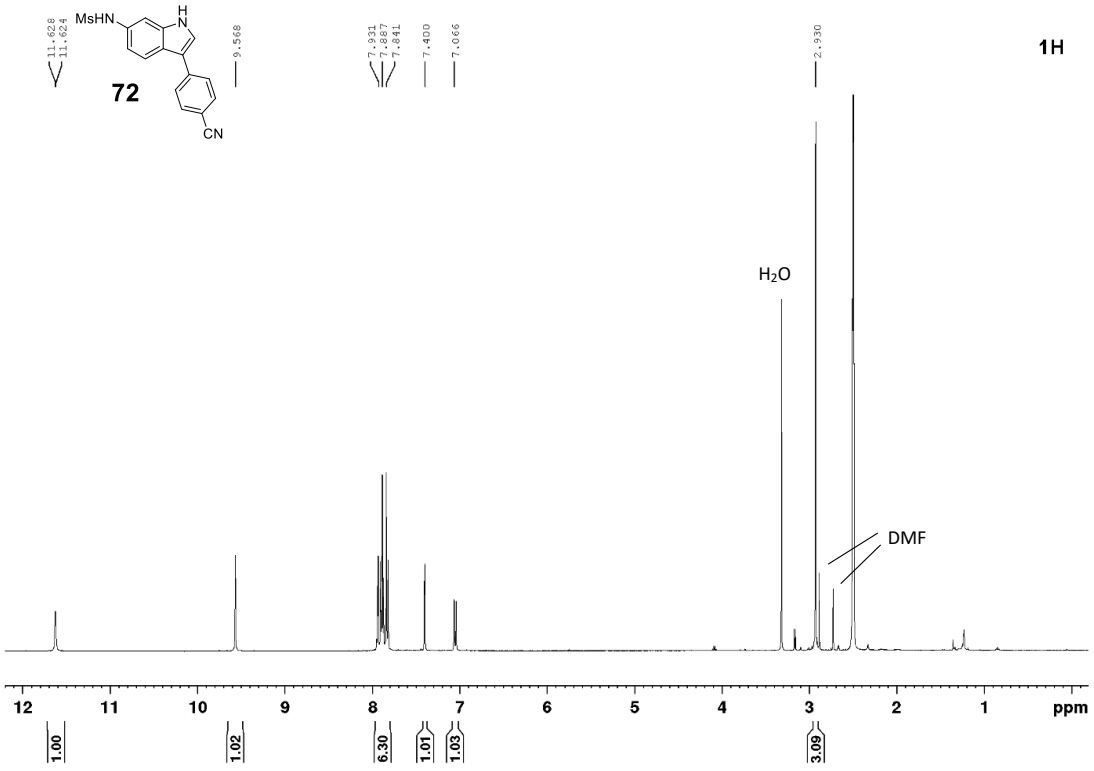

1H
69.c
11.549
7.446
7.377
7.302
7.146
7.077
6.982
1.943
H2O
7.4
7.2
ppm
0.92
1.00
1.97
7.00
1.05
1.03
1.01
2.97

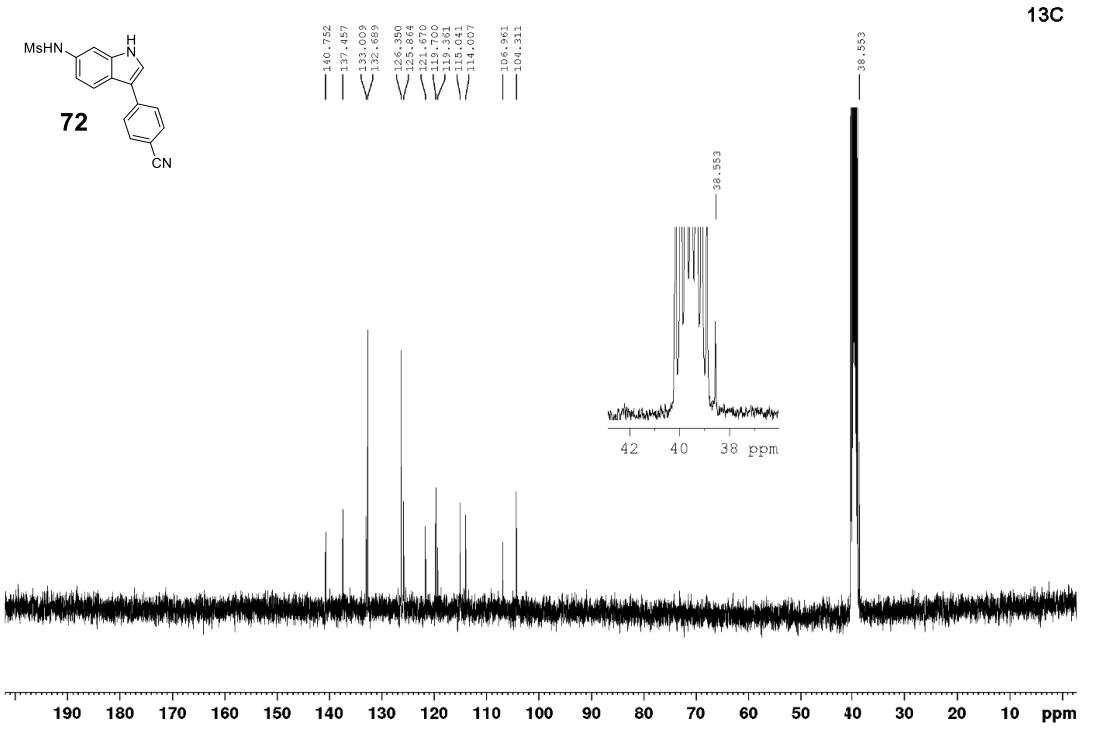

13C
69.c
136.917
134.092
133.589
132.730
131.167
130.215
128.679
128.529
127.191
127.138
126.633
126.026
121.876
119.398
118.704
112.956
111.372
19.770

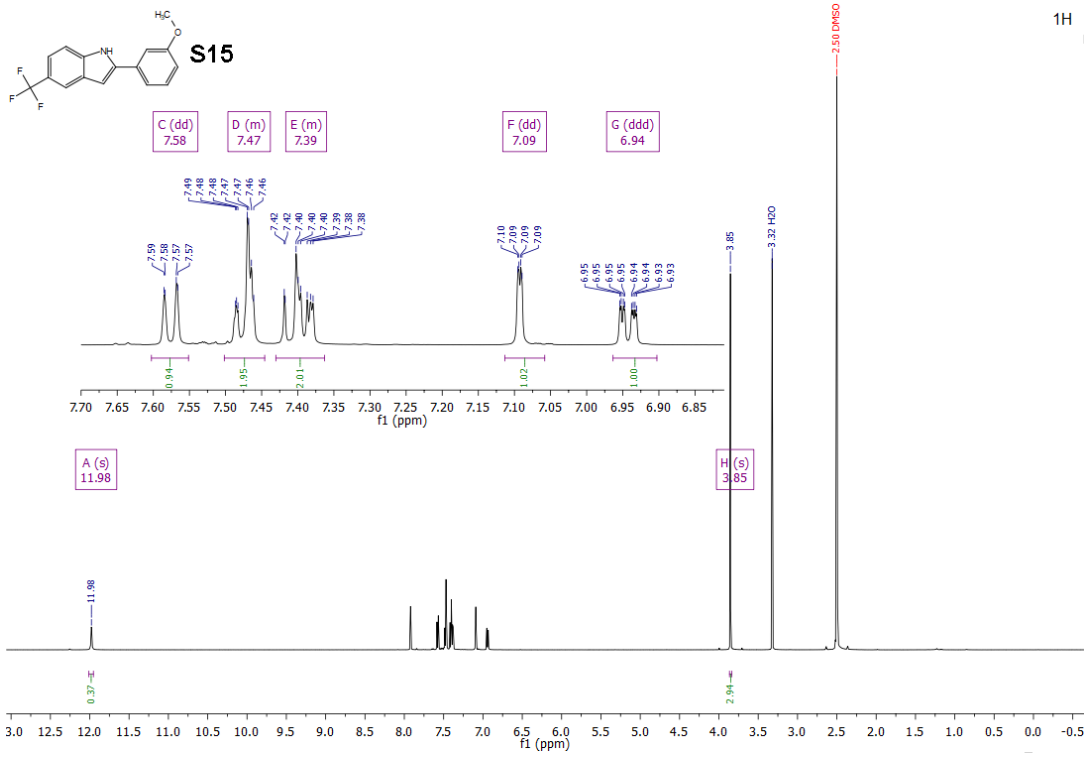

1H
11.503
7.449
7.360
7.289
7.221
7.151
7.029
2.342
69.e
H2O
7.4
7.2
ppm
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.91
3.85
1.97
1.03
3.85
1.04
1.00
2.88

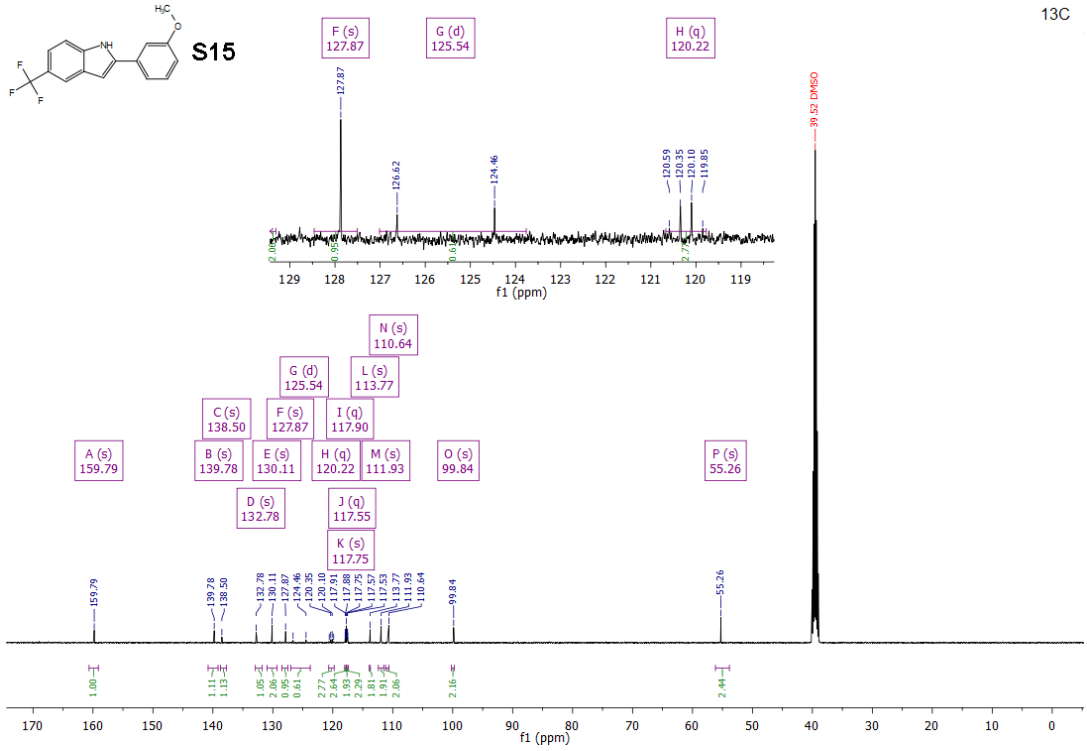

13C
69.e
136.060
135.085
133.809
132.351
132.220
129.598
129.266
128.776
128.072
127.409
121.914
119.589
118.597
113.196
111.427
20.798
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

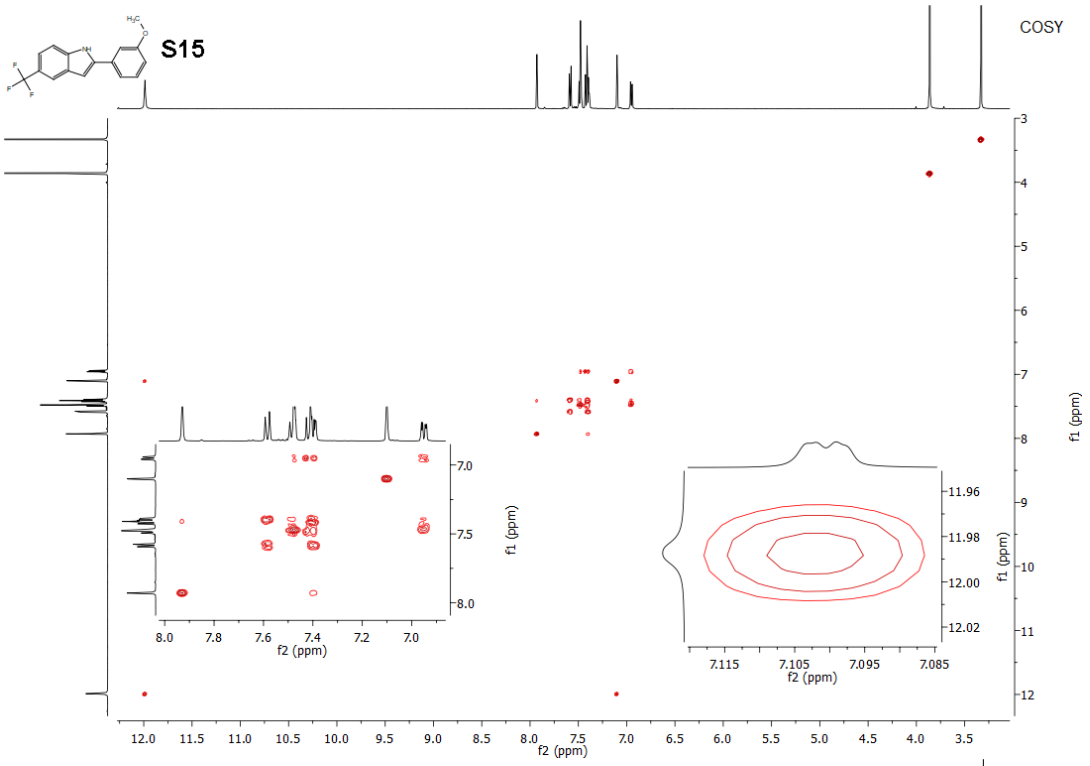

1H
69.f
1 eq EtOAc
H2O
ppm
13C
69.f
EtOAc
EtOAc

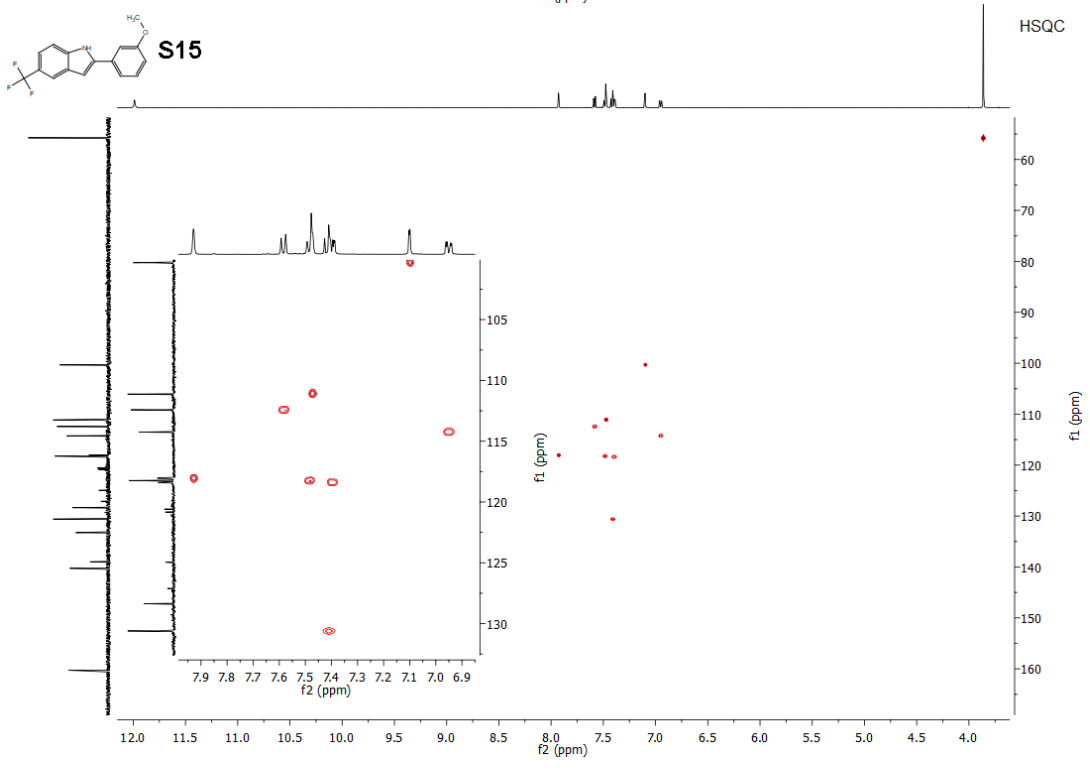

1H
MsHN
H
N
72
CN
11.628
11.624
9.568
7.931
7.887
7.841
7.400
7.066
2.930
H2O
DMF
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
6.30
1.01
1.03
3.09

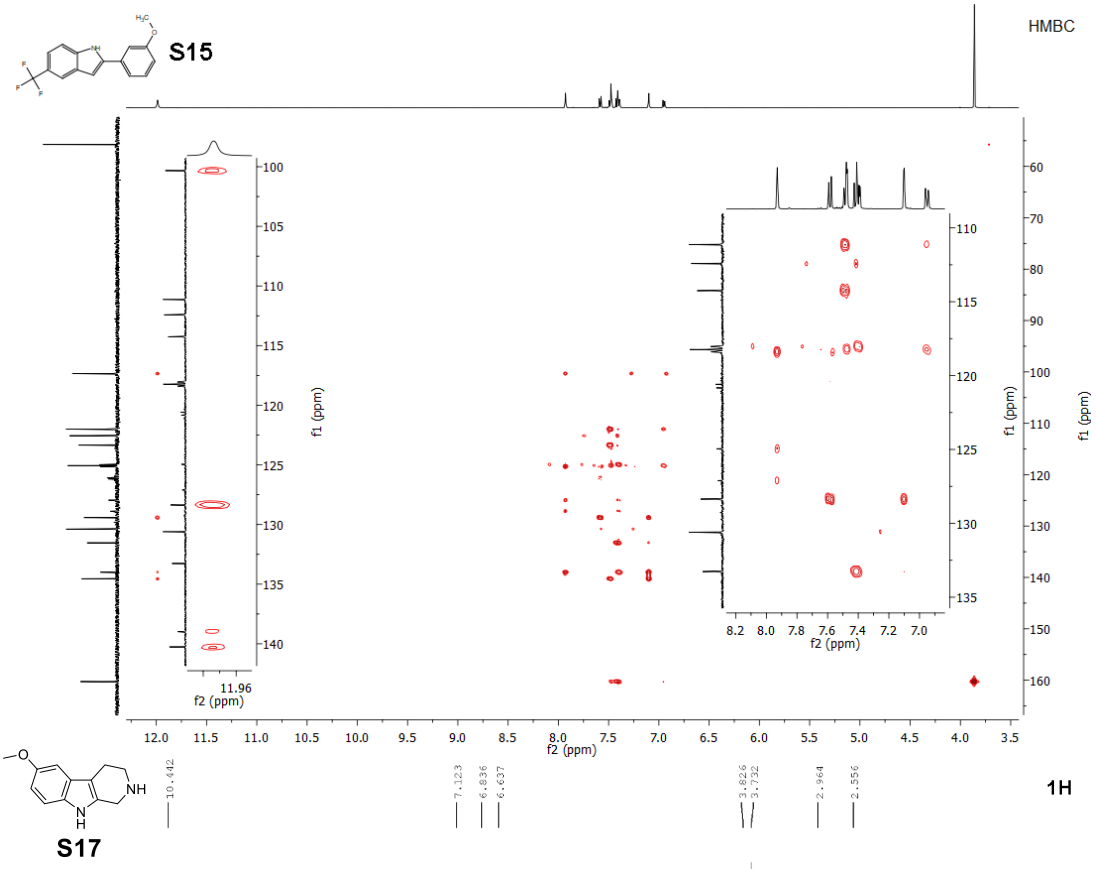

13C
MsHN
H
N
72
CN
140.752
137.457
133.009
132.689
126.350
125.864
121.670
119.700
119.341
115.041
114.007
106.961
104.311
38.553
38.553
42
40
38 ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


S15
1H
C (dd) 7.58
D (m) 7.47
E (m) 7.39
F (dd) 7.09
G (ddd) 6.94
A (s) 11.98
H (s) 3.85
2.50 DMSO
3.32 H2O
f1 (ppm)


S15
13C
F (s) 127.87
G (d) 125.54
H (q) 120.22
N (s) 110.64
L (s) 113.77
C (s) 138.50
I (q) 117.90
A (s) 159.79
B (s) 139.78
E (s) 130.11
M (s) 111.93
O (s) 99.84
P (s) 55.26
D (s) 132.78
J (q) 117.55
K (s) 117.75
39.52 DMSO
f1 (ppm)


S15
COSY
f2 (ppm)
f1 (ppm)

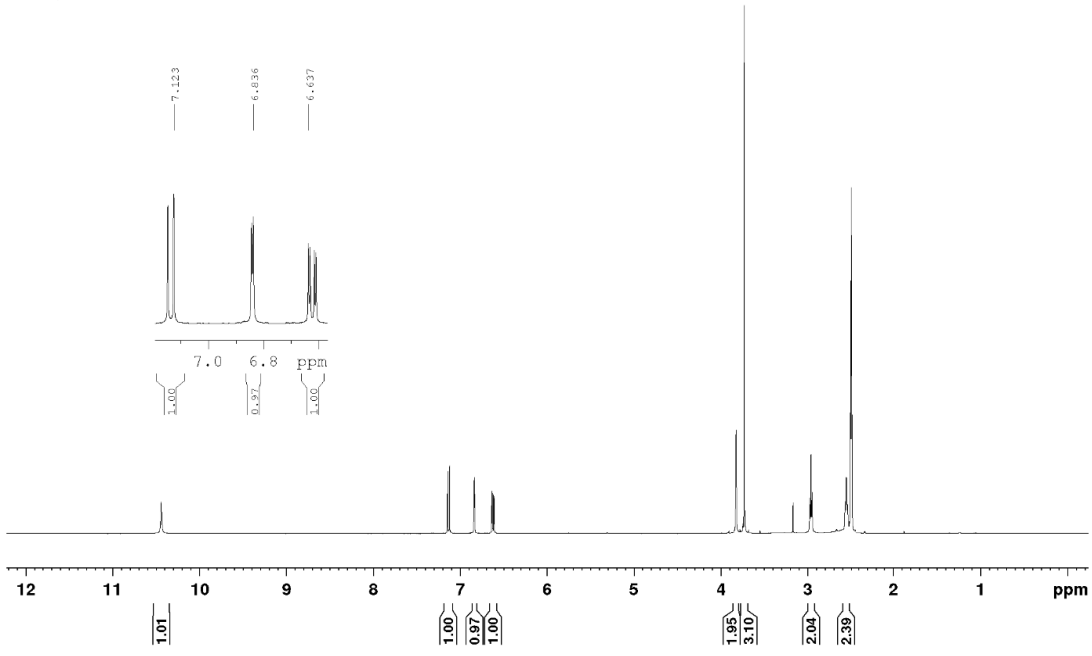

S15
HSQC
f2 (ppm)
f1 (ppm)

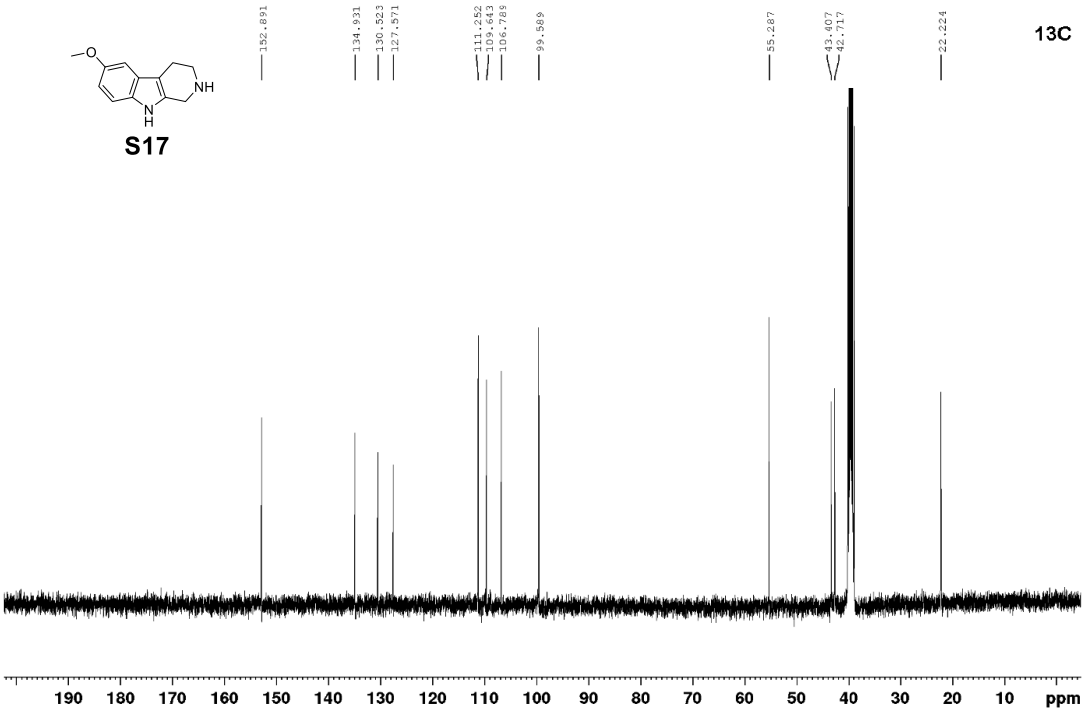

S15
HMBC
f1 (ppm)
f2 (ppm)
11.96
8.2 8.0 7.8 7.6 7.4 7.2 7.0
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5

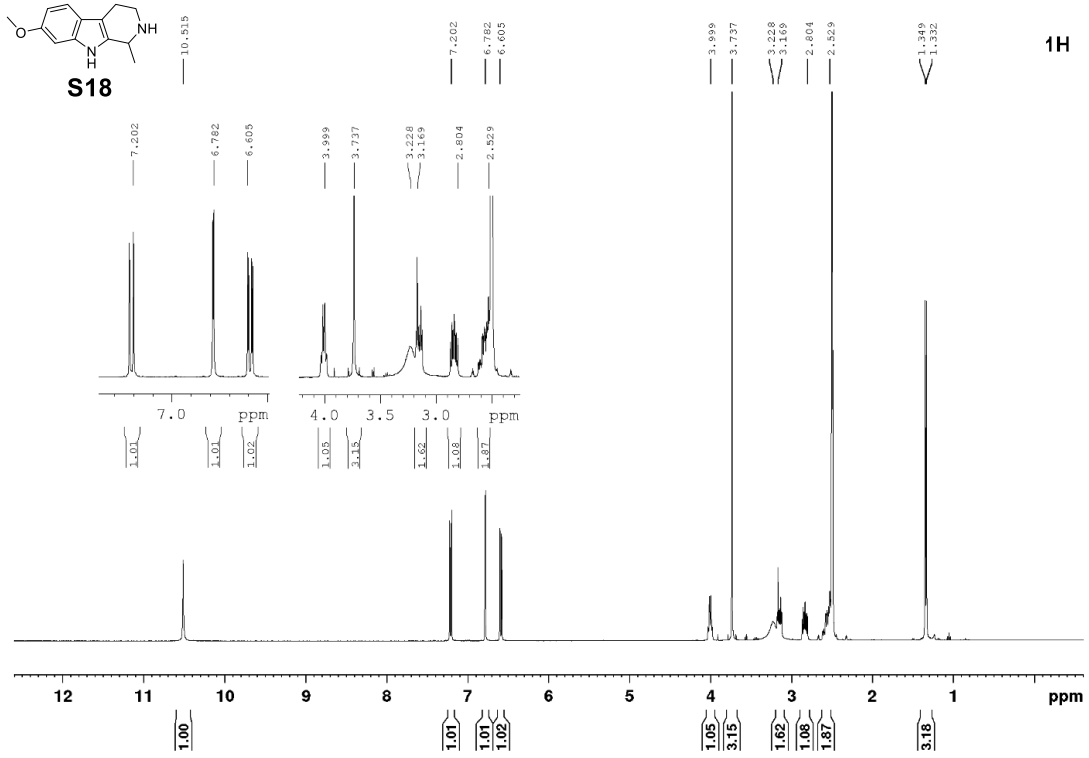
NH
S17

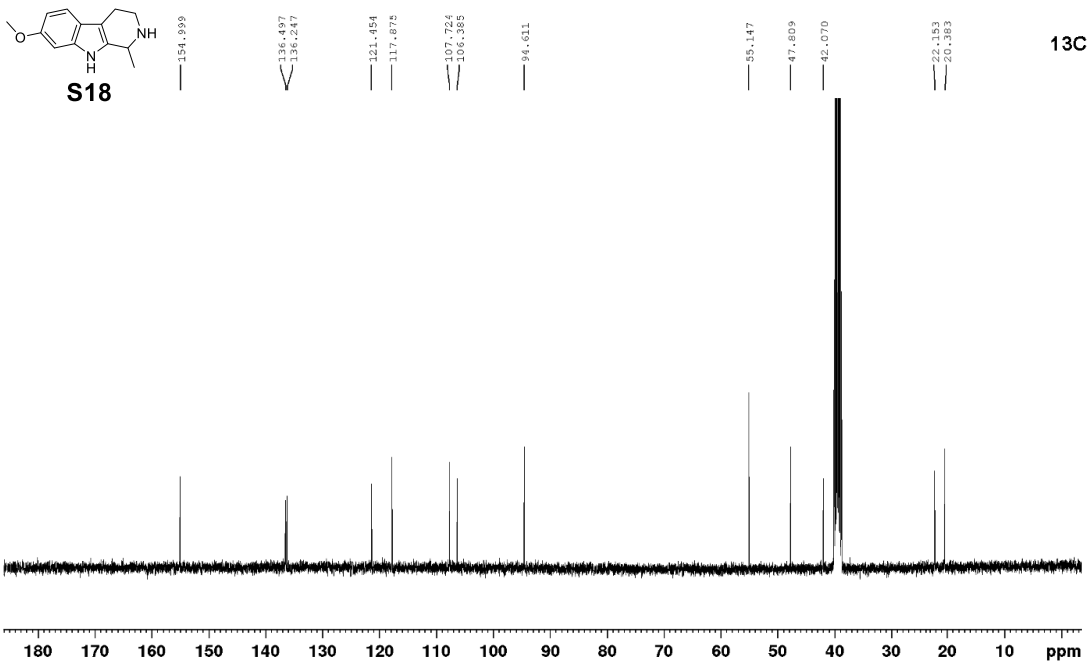
10.442
7.123
6.836
6.637
3.826
3.732
2.964
2.556

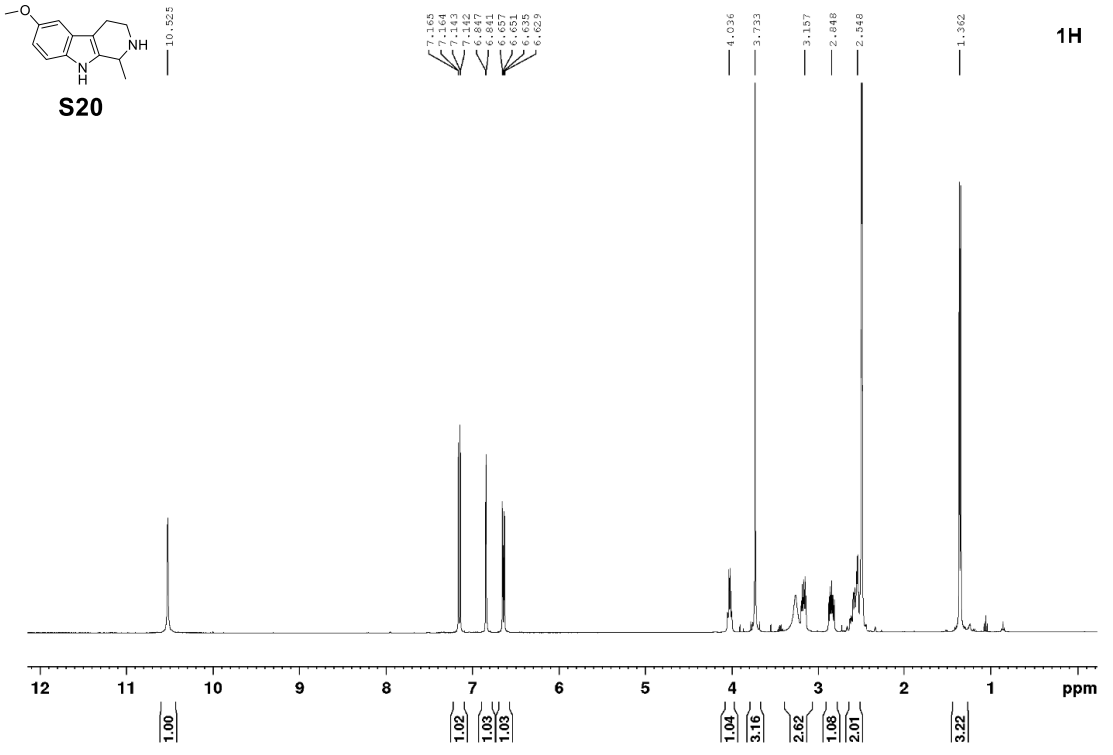
1H

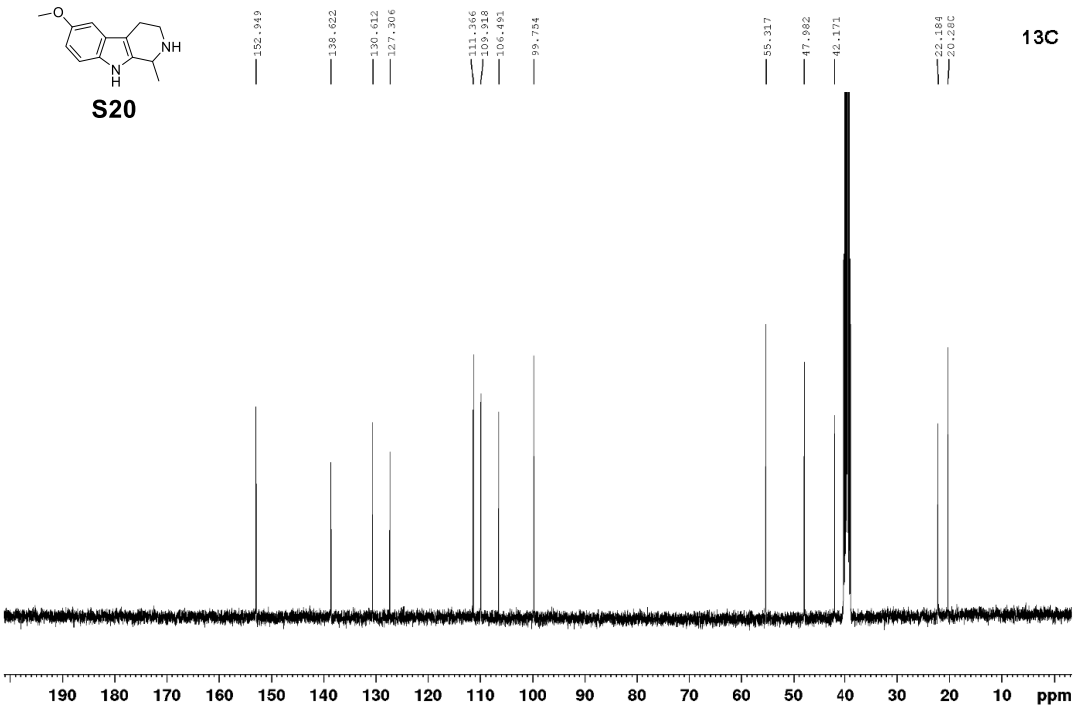

7.123
6.836
6.637
7.0 6.8 ppm
1.00
0.97
1.00
12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.01
1.00
0.97
1.00
1.95
3.10
2.04
2.39

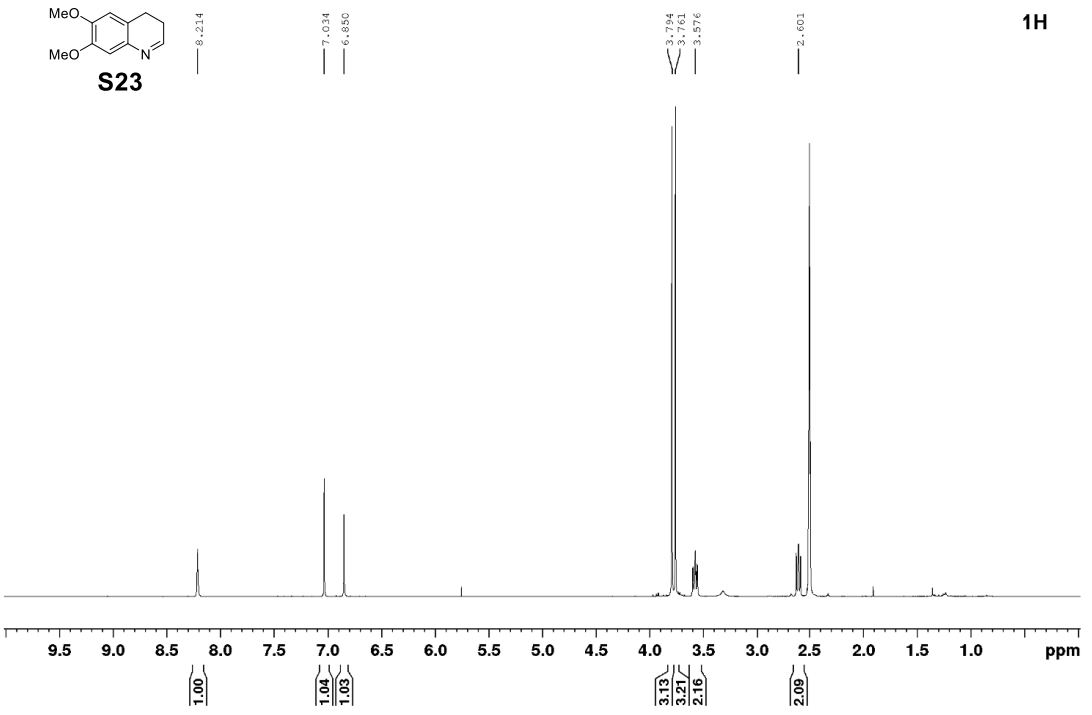

S17
152.891
134.931
130.523
127.571
111.252
109.643
106.785
99.589
55.287
43.407
42.717
22.224
13C
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

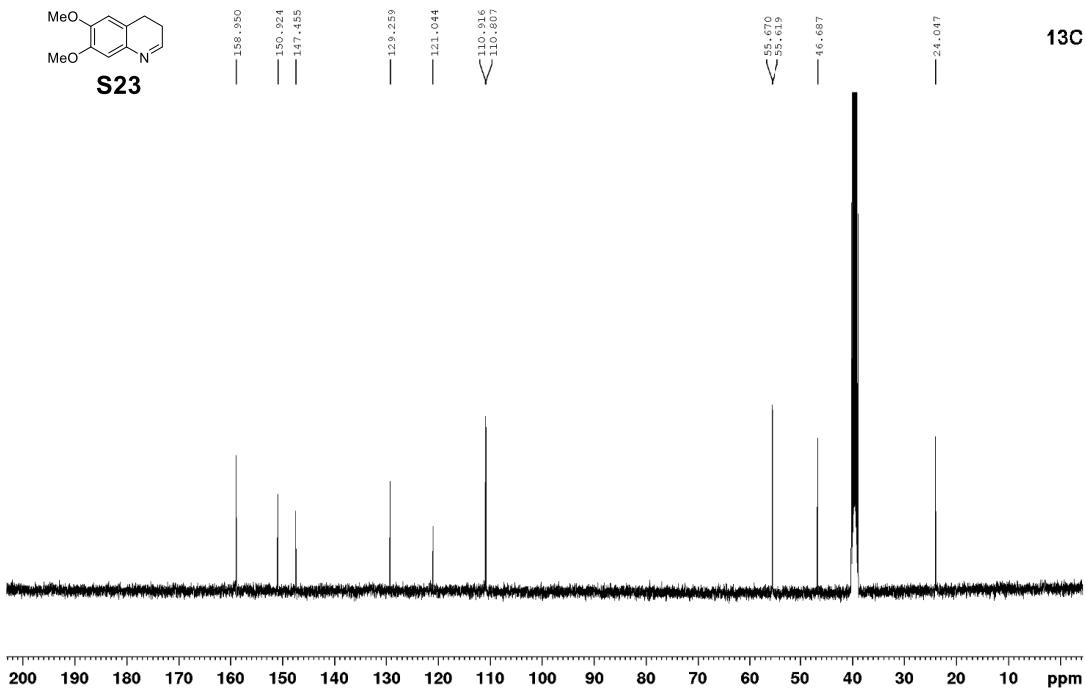

S18
10.515
7.202
6.782
6.605
3.999
3.737
3.228
3.169
2.804
2.529
1.349
1.332
1H
7.0 ppm
4.0 3.5 3.0 ppm
12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.01
1.01
1.02
1.05
3.15
1.62
1.08
1.87
3.18


S18
154.999
136.497
136.247
121.454
117.875
107.724
106.365
94.611
55.147
47.809
42.070
22.153
20.383
13C
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


S20
10.525
7.165
7.164
7.143
7.142
6.847
6.841
6.657
6.651
6.635
6.629
4.036
3.733
3.157
2.648
2.548
1.362
1H
12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.02
1.03
1.03
1.04
3.16
2.62
1.08
2.01
3.22


S20
152.949
138.622
130.612
127.306
111.366
109.918
106.491
99.754
55.317
47.982
42.171
22.184
20.280
13C
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


MeO
MeO
N
S23
8.214
7.034
6.850
3.794
3.761
3.576
2.601
1H
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.04
1.03
3.13
3.21
2.16
2.09


MeO
MeO
N
S23
158.950
150.924
147.455
129.259
121.044
110.916
110.807
55.670
55.619
46.687
24.047
13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm